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(54) **AZOLE COMPOUNDS**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2002/0103185 A1* 8/2002 Sanner et al. 514/217.09

FOREIGN PATENT DOCUMENTS

EP 0526877 A2 2/1993
EP 0630894 A1 12/1994
EP 0987265 A1 3/2000
GB 1425505 A 2/1976
JP 52-083747 7/1977
JP 71014458 8/1993

WO WO 97/36882 10/1997
WO WO 99/02505 1/1999
WO WO 00/01679 1/2000
WO WO 01/10866 A1 2/2001
WO WO 01/14372 A2 3/2001
WO WO 01/77101 A1 10/2001
WO WO 02/20484 A1 3/2002
WO WO 03/000257 A1 1/2003

OTHER PUBLICATIONS

Ushijima et al. Analytical Science & Technology 1995, 8(4), 545-51. *CAS Abstract attached.*
Saito et al. Journal of Chromatography, B: Biomedical Applications 1995, 674(2), 167-75. *CAS Abstract attached.*
Saito et al. Analytical Sciences 1994, 10(4), 679-81. *CAS Abstract attached.*
T. Jakobiec, et al., "Synthesis of Derivatives of 2-Amino-4-P-Chlorophenylthiazole-5-Acetic Acid", Archivum Immunologiae et Therapiae Experimentalis, (1978), pp. 935-941, vol. 26.
S. Bengtsson, et al., "Compounds Related to Clomethiazole—VI. Synthesis of Some Reference Compounds in Connection with Biotransformation Studies", Acta Pharm. Suec., (1982), pp. 37-42, vol. 19, No. 1.

* cited by examiner

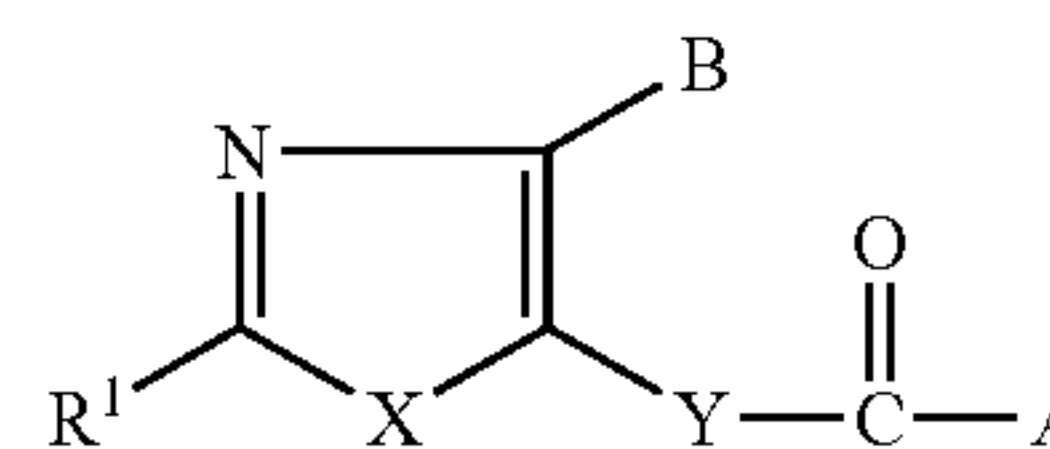
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(57) **ABSTRACT**

The present invention provides a compound represented by the formula (I)



wherein R¹ is a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group,

A is an optionally substituted cyclic amino group or —NR²—W—D wherein R² is a hydrogen atom or an alkyl group, W is a bond or a divalent acyclic hydrocarbon group, and D is an optionally substituted cyclic group, an optionally substituted amino group or an optionally substituted acyl group,

B is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group,

X is an oxygen atom, a sulfur atom or an optionally substituted nitrogen atom, and

Y is a bond or a divalent acyclic hydrocarbon group, or a salt thereof, which is useful for the prophylaxis or treatment of diabetic neuropathy and the like.

10 Claims, No Drawings

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AZOLE COMPOUNDS

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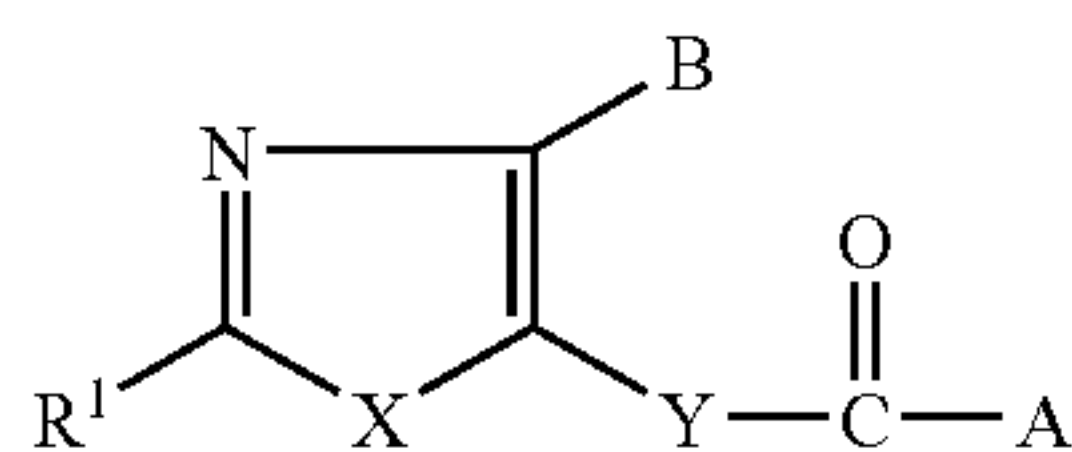
TECHNICAL FIELD

The present invention relates to an azole compound having a promoting action on the production or secretion of a neurotrophic factor and useful for the prophylaxis or treatment of diabetic neuropathy and the like.

BACKGROUND ART

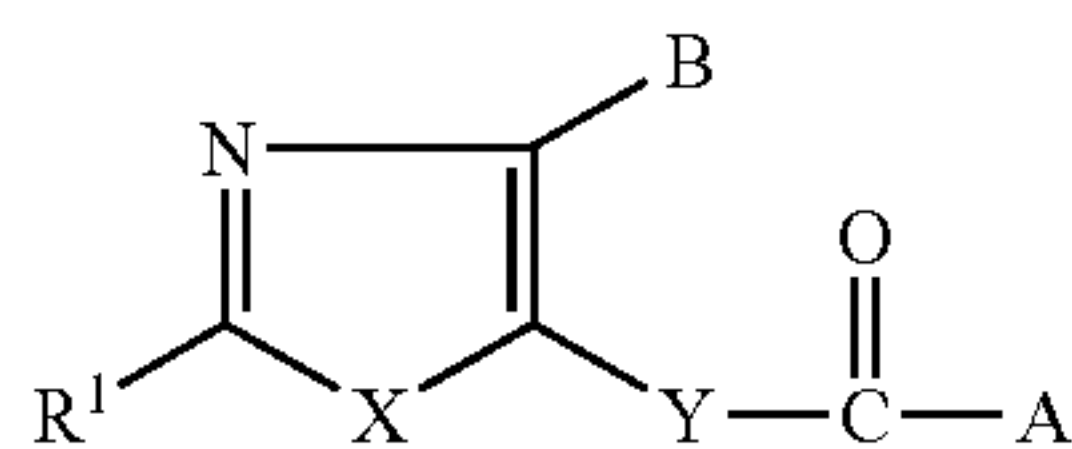
Azole compounds are described in, for example, the following references.

(1) WO97/36882 describes that a compound represented by the formula



wherein R¹ is a halogen atom, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group, A is an optionally substituted acyl group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group or an optionally esterified or amidated carboxyl group, B is an optionally substituted aromatic group and Y is a divalent aliphatic hydrocarbon group is useful as an agent for the prophylaxis or treatment of diabetes.

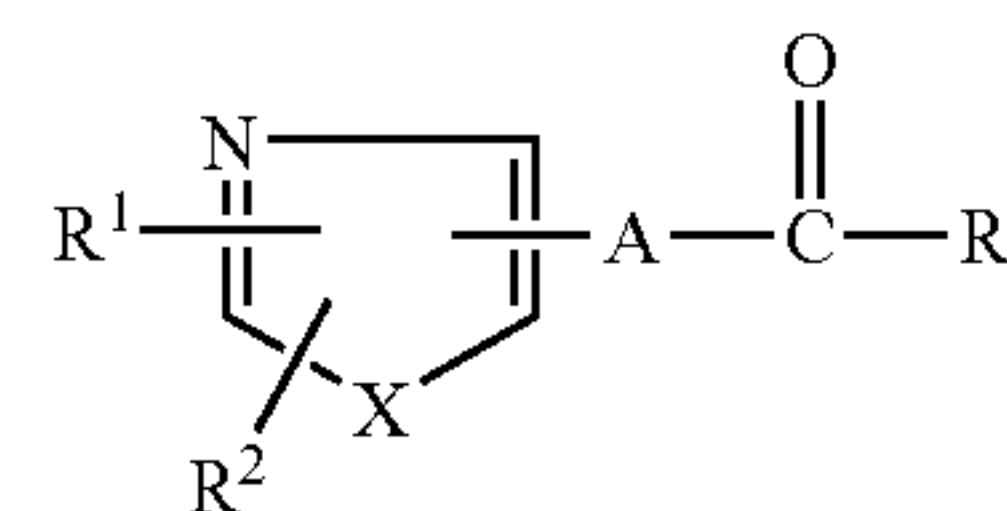
(2) WO01/14372 describes that a compound represented by the formula



wherein R¹ is a halogen atom, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group, A is an optionally substituted acyl group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group or an optionally esterified or amidated carboxyl group, B is an optionally substituted aromatic group, X is an oxygen atom, a sulfur atom or an optionally substituted nitrogen atom, and Y is a divalent hydrocarbon group or heterocyclic group is useful as a neurotrophin production or secretion promoter.

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(3) WO00/01679 describes that a compound represented by the formula



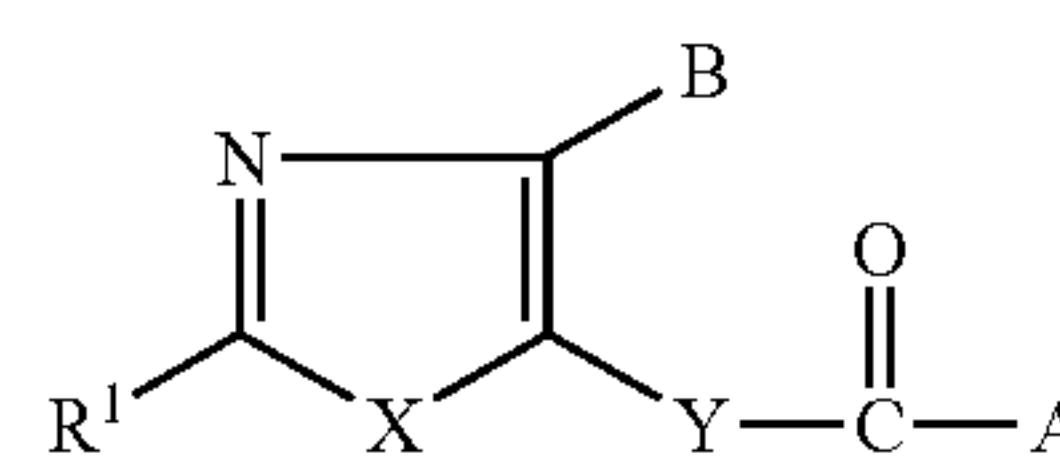
wherein R¹ is an aromatic hydrocarbon group or an aromatic heterocyclic group, each of which is optionally substituted; R² is a hydrogen or an optionally substituted hydrocarbon group;

X is O, S or a group represented by —NR⁴— wherein R⁴ is a hydrogen or an optionally substituted alkyl group; A is an aromatic hydrocarbon group or an aromatic heterocyclic group, each of which is optionally substituted; R³ is a group represented by the formula —OR⁵ wherein R⁵ is a hydrogen or an optionally substituted hydrocarbon group or —NR⁶R⁷ wherein R⁶ and R⁷ are the same or different and each is a hydrogen or an optionally substituted hydrocarbon group, and R⁶ and R⁷ may form a ring together with the adjacent nitrogen atom is useful as a retinoid-related receptor function regulator.

DISCLOSURE OF THE INVENTION

An object of the present invention is to provide an azole compound having a superior promoting action on the production or secretion of a neurotrophic factor and is of lower toxicity.

The present inventors have found that a compound represented by the formula (I)



wherein R¹ is a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group,

B is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group,

X is an oxygen atom, a sulfur atom or an optionally substituted nitrogen atom,

A is an optionally substituted cyclic amino group or —NR²—W—D wherein R² is a hydrogen atom or an alkyl group, W is a bond or a divalent acyclic hydrocarbon group, and D is an optionally substituted cyclic group, an optionally substituted amino group or an optionally substituted acyl group, and

Y is a bond or a divalent acyclic hydrocarbon group, which is structurally characterized in that a group represented by the formula: —Y—CO—A wherein A and Y are as defined above, is bonded at the 5-position of an azole ring has, based on the characteristic chemical structure, a superior neurotrophic factor producing or secreting action, and completed the present invention based on this finding.

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Accordingly, the present invention relates to

- 1) a compound represented by the formula (I) or a salt thereof (hereinafter sometimes to be abbreviated as compound (I));
- 2) the compound (I) wherein R¹ is an optionally substituted heterocyclic group;
- 3) the compound (I) wherein A is an optionally substituted cyclic amino group;
- 4) the compound (I) wherein A is —NR²—W—D wherein R² is a hydrogen atom or an alkyl group, W is a bond or a divalent acyclic hydrocarbon group, and D is an optionally substituted cyclic group, an optionally substituted amino group or an optionally substituted acyl group;
- 5) the compound of the aforementioned 4), wherein D is an optionally substituted cyclic group;
- 6) the compound (I) wherein B is an optionally substituted C₆₋₁₄ aryl group;
- 7) the compound (I) wherein X is an oxygen atom;
- 8) the compound (I) wherein Y is C₁₋₄ alkylene;
- 9) the compound (I) which is 3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide, 3-[4-(4-chlorophenyl)-2-(4-morpholinyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide, 3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-(dimethylphosphonomethyl)phenyl]propionamide, 3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide, 4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(dimethylphosphonomethyl)phenyl]butanamide, 1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol, 4-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide, 4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]butanamide, or 4-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide; 10) a pharmaceutical agent comprising compound (I) or a prodrug thereof;
- 11) the pharmaceutical agent of the aforementioned 10), which is an agent for the prophylaxis or treatment of diabetic neuropathy;
- 12) the pharmaceutical agent of the aforementioned 10), which is an agent for ameliorating pain;
- 13) an agent for promoting production or secretion of a neurotrophic factor which comprises compound (I) or a prodrug thereof;
- 14) use of compound (I) or a prodrug thereof for the production of an agent for the prophylaxis or treatment of diabetic neuropathy;
- 15) a method for the prophylaxis or treatment of diabetic neuropathy in a mammal, which comprises administering an effective amount of compound (I) or a prodrug thereof to the mammal;
- 16) use of compound (I) or a prodrug thereof for the production of an agent for ameliorating pain;
- 17) a method for ameliorating pain in a mammal, which comprises administering an effective amount of compound (I) or a prodrug thereof to the mammal;
- 18) use of compound (I) or a prodrug thereof for the production of an agent for promoting production or secretion of a neurotrophic factor;

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19) a method for promoting production or secretion of a neurotrophic factor in a mammal, which comprises administering an effective amount of compound (I) or a prodrug thereof to the mammal; and the like.

The compound represented by the formula (I) is described in detail in the following.

In the formula (I), as the “halogen atom” for R¹, for example, a fluorine atom, a chlorine atom, a bromine atom and an iodine atom can be mentioned. Of these, a fluorine atom and a chlorine atom are preferable.

As the “hydrocarbon group” in the “optionally substituted hydrocarbon group” for R¹, for example, an aliphatic hydrocarbon group, an alicyclic hydrocarbon group, an aromatic hydrocarbon group, an aromatic aliphatic hydrocarbon group, an alicyclic aliphatic hydrocarbon group and the like can be mentioned.

As the aliphatic hydrocarbon group, for example, a straight-chain or branched aliphatic hydrocarbon group having 1 to 15 carbon atoms, specifically an alkyl group, an alkenyl group, an alkynyl group and the like can be mentioned.

As preferable examples of the alkyl group, C₁₋₁₀ alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, heptyl, octyl, nonyl, decyl and the like can be mentioned.

As preferable examples of the alkenyl group, C₂₋₁₀ alkenyl groups such as ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 3-hexenyl, 5-hexenyl, 1-heptenyl, 1-octenyl and the like can be mentioned.

As preferable examples of the alkynyl groups, C₂₋₁₀ alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptyne, 1-octyne and the like can be mentioned.

As the alicyclic hydrocarbon group, for example, a saturated or unsaturated alicyclic hydrocarbon group having 3 to 12 carbon atoms, specifically a cycloalkyl group, a cycloalkenyl group, a cycloalkadienyl group and the like, can be mentioned.

As preferable examples of the cycloalkyl group, C₃₋₁₀ cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl, bicyclo[4.3.1]decyl and the like can be mentioned.

As preferable examples of the cycloalkenyl group, C₃₋₁₀ cycloalkenyl groups such as 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl and the like can be mentioned.

As preferable examples of the cycloalkadienyl group, C₄₋₁₀ cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl and the like can be mentioned.

As the aromatic hydrocarbon group, for example, a C₆₋₁₄ aryl group and the like can be mentioned. As preferable examples of the aryl group, phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl, biphenyl, indenyl and the like can be mentioned. Of these, phenyl, naphthyl and the like are preferable. The aryl group may be partially saturated and as the partially saturated aryl group, for example, dihydroindenyl, tetrahydronaphthyl and the like can be mentioned.

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As the aromatic aliphatic hydrocarbon group, for example, a C_{7-14} aromatic aliphatic hydrocarbon group, and concretely, an aralkyl group, an arylalkenyl group, an arylalkynyl group and the like can be mentioned.

As preferable examples of the aralkyl group, C_{7-14} aralkyl groups such as benzyl, phenethyl, naphthylmethyl, benzhydryl, phenylpropyl, phenylbutyl, diphenylethyl and the like can be mentioned.

As preferable examples of the arylalkenyl group, C_{8-13} arylalkenyl groups such as styryl and the like can be mentioned.

As preferable examples of the arylalkynyl group, C_{8-13} arylalkynyl groups such as phenylethynyl and the like can be mentioned.

As the alicyclic aliphatic hydrocarbon group, for example, a C_{4-13} alicyclic aliphatic hydrocarbon group, and concretely, a cycloalkylalkyl group, a cycloalkylalkenyl group, a cycloalkenylalkyl group and the like can be mentioned.

As preferable examples of the cycloalkylalkyl group, C_{4-13} cycloalkylalkyl groups such as cyclopropylmethyl, cyclopropylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl and the like can be mentioned.

As preferable examples of the cycloalkylalkenyl group, C_{5-13} cycloalkylalkenyl groups such as cyclopropylethenyl, cyclopentylethenyl, cyclohexylethenyl and the like can be mentioned.

As preferable examples of the cycloalkenylalkyl group, C_{4-13} cycloalkenylalkyl groups such as cyclopentenylmethyl, cyclopentenylethyl, cyclohexenylmethyl, cyclohexenylethyl and the like can be mentioned.

The above-mentioned "optionally substituted hydrocarbon group" for R^1 may have 1 to 3 substituent(s) at substitutable position(s). As such substituent, for example, a halogen atom, a nitro, an oxo, a C_{1-3} alkylendioxy, an optionally substituted aromatic heterocyclic group, an optionally substituted non-aromatic heterocyclic group, an optionally substituted amino group, an optionally substituted hydroxy group, an optionally substituted thiol group, an optionally substituted acyl group and the like can be mentioned.

As the halogen atoms, for example, a fluorine atom, a chlorine atom, a bromine atom and an iodine atom can be mentioned. Especially preferred are a fluorine atom and a chlorine atom.

As the C_{1-3} alkylendioxy, for example, methylenedioxy, ethylenedioxy and the like can be mentioned.

As the "aromatic heterocyclic group" of the "optionally substituted aromatic heterocyclic group", for example, a 5- to 7-membered monocyclic aromatic heterocyclic group which contains, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a condensed aromatic heterocyclic group can be mentioned. As the condensed aromatic heterocyclic group, for example, a group wherein the 5- to 7-membered monocyclic aromatic heterocyclic group is condensed with a 6-membered ring containing 1 or 2 nitrogen atom(s), a benzene ring, a 5-membered ring containing 1 sulfur atom, and the like can be mentioned.

As preferable examples of the "aromatic heterocyclic group", furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g., 2-pyrazinyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyra-

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zoyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl, thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl), thiadiazolyl (e.g., 1,3,4-thiadiazol-2-yl), triazolyl (e.g., 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl, tetrazol-5-yl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl), quinazolyl (e.g., 2-quinazolyl, 4-quinazolyl), quinoxalyl (e.g., 2-quinoxalyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl), benzothienyl (e.g., 2-benzothienyl, 3-benzothienyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), benzimidazolyl (e.g., benzimidazol-1-yl, benzimidazol-2-yl), indolyl (e.g., indol-1-yl, indol-3-yl), 1H-indazolyl (e.g., 1H-indazol-3-yl), 1H-pyrrolo[2,3-b]pyrazinyl (e.g., 1H-pyrrolo[2,3-b]pyrazin-2-yl), 1H-pyrrolopyridinyl (e.g., 1H-pyrrolo[2,3-b]pyridin-6-yl), 1H-imidazopyridinyl (e.g., 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl), 1H-imidazopyrazinyl (e.g., 1H-imidazo[4,5-b]pyrazin-2-yl), triazinyl, isoquinolyl, benzoxadiazolyl, benzothiadiazolyl, benztriazolyl and the like can be mentioned.

As the "non-aromatic heterocyclic group" of the "optionally substituted non-aromatic heterocyclic group", for example, a 5- to 7-membered monocyclic non-aromatic heterocyclic group which contains, as a ring-constituting atom besides carbon atoms, 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom, and a condensed non-aromatic heterocyclic group can be mentioned. As the condensed non-aromatic heterocyclic group, for example, a group wherein the 5- to 7-membered monocyclic non-aromatic heterocyclic group is condensed with a 6-membered ring containing 1 or 2 nitrogen atom(s), a benzene ring, a 5-membered ring containing 1 sulfur atom, and the like can be mentioned.

As preferable examples of the non-aromatic heterocyclic group, pyrrolidinyl (e.g., 1-pyrrolidinyl), piperidinyl (e.g., piperidino), morpholinyl (e.g., morpholino), thiomorpholinyl (e.g., thiomorpholino), piperazinyl (e.g., 1-piperazinyl), hexamethyleniminyl (e.g., hexamethylenimin-1-yl), oxazolidinyl (e.g., oxazolidin-3-yl), thiazolidinyl (e.g., thiazolidin-3-yl), imidazolidinyl (e.g., imidazolidin-3-yl), imidazolyl (e.g., imidazolin-1-yl, imidazolin-2-yl), oxazolyl (e.g., oxazolin-2-yl), thiazolyl (e.g., thiazolin-2-yl), oxazinyl (e.g., oxazin-2-yl), tetrahydrofuranyl, azepanyl, tetrahydropyridinyl (e.g., 1,2,3,6-tetrahydropyridin-1-yl), dihydrobenzofuranyl, dioxolanyl, dithiolanyl, tetrahydroisoquinolyl and the like can be mentioned.

The above-mentioned aromatic heterocyclic group and non-aromatic heterocyclic group may have 1 to 3 substituent(s) at substitutable position(s). As such substituent, for example, a nitro, a hydroxy, an amino, an oxo, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C_{1-6} alkyl (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C_{1-6} alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C_{6-14} aryl (e.g., phenyl) and the like can be mentioned.

As the "optionally substituted amino group", for example, an amino group optionally mono- or di-substituted by a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{3-10} cycloalkyl group, a C_{3-10} cycloalkenyl group, a C_{6-14} aryl group, a C_{7-14} aralkyl, a C_{1-15} acyl group or a heteroaryl group, each of which is optionally substituted can be mentioned.

Here, as the C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{3-10} cycloalkyl group, C_{3-10} cycloalkenyl group, C_{6-14} aryl group

and C₇₋₁₄ aralkyl, those exemplified for the “hydrocarbon group” of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

As the C₁₋₁₅ acyl group, those exemplified for the acyl group of the “optionally substituted acyl group” to be mentioned later can be mentioned. The acyl group is preferably a formyl, a C₁₋₁₀ alkyl-carbonyl, a C₁₋₆ alkoxy-carbonyl, a C₆₋₁₄ aryl-carbonyl, a C₇₋₁₃ aralkyl-carbonyl, an aromatic heterocyclic-carbonyl, a 5- to 7-membered non-aromatic heterocyclic-carbonyl, a C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclopentanecarbonyl, cyclohexanecarbonyl); a C₈₋₁₃ arylalkenyl-carbonyl (e.g., styrylcarbonyl); a C₈₋₁₃ arylalkynyl-carbonyl (e.g., phenylethynylcarbonyl); a C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl); a mono- or di-C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl, tert-butylcarbamoyl); a C₃₋₁₀ cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl); a C₆₋₁₄ aryl-carbamoyl (e.g., phenylcarbamoyl); a C₇₋₁₄ aralkyl-carbamoyl (e.g., benzylcarbamoyl, phenethylcarbamoyl, diphenylethylcarbamoyl); a C₄₋₁₃ cycloalkylalkyl-carbamoyl (e.g., cyclohexylmethylcarbamoyl); an aromatic heterocyclic carbamoyl (e.g., isoxazolylcarbamoyl, benzothiazolylcarbamoyl); a non-aromatic heterocyclic carbamoyl (e.g., pyrrolidinylcarbamoyl); a C₇₋₁₄ aralkyloxy-carbamoyl (e.g., benzyloxycarbamoyl); and the like. As the C₁₋₁₅ acyl group, moreover, a C₁₋₆ alkoxy-carbamoyl (e.g., methoxycarbamoyl), a C₁₋₆ alkoxy-carbonylcarbamoyl (e.g., methoxycarbonylcarbamoyl, ethoxycarbonylcarbamoyl) and the like can be also mentioned.

As preferable examples of the C₁₋₁₀ alkyl-carbonyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl and the like can be mentioned.

As preferable examples of the C₁₋₆ alkoxy-carbonyl, for example, tert-butoxycarbonyl and the like can be mentioned.

As preferable examples of the C₆₋₁₄ aryl-carbonyl, benzoyl and the like can be mentioned.

As preferable examples of the C₇₋₁₃ aralkyl-carbonyl, benzylcarbonyl, phenethylcarbonyl and the like can be mentioned.

As preferable examples of the aromatic heterocyclic-carbonyl, furylcarbonyl, pyrrolylcarbonyl, thienylcarbonyl, pyridylcarbonyl, pyrimidinylcarbonyl, 1H-indazolylcarbonyl, benzofuranylcarbonyl, quinolylcarbonyl and the like can be mentioned.

As preferable examples of the 5 to 7-membered non-aromatic heterocyclic-carbonyl, tetrahydrofurylcarbonyl, thiomorpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl, hexamethyleniminylcarbonyl, thiazolidinylcarbonyl and the like can be mentioned.

As the heteroaryl group, for example, the aromatic heterocyclic groups exemplified for the substituents of the “optionally substituted heterocyclic group” for R¹ can be mentioned. Of these, pyridyl, imidazolyl, triazolyl, pyrimidinyl and the like are preferable.

The C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group, C₇₋₁₄ aralkyl, C₁₋₁₅ acyl group and heteroaryl group may have 1 or 2 substituent(s) at substitutable position(s). As such substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a hydroxy; a nitro; an amino group optionally mono- or di-substituted by C₁₋₆ alkyl group (e.g., methyl); a

C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl); oxo; cyano; a C₇₋₁₃ aralkyl group (e.g., benzyl); a C₁₋₆ alkoxy-carbonylamino-C₁₋₆ alkyl group (e.g., methoxycarbonylaminoethyl, ethoxycarbonylaminoethyl); a mono- or di-C₁₋₁₀ alkylphosphono-C₁₋₆ alkyl group (e.g., dimethylphosphonomethyl, diethylphosphonomethyl); a mono- or di-C₁₋₆ alkylamino-C₁₋₆ alkyl group (e.g., dimethylaminomethyl); a C₁₋₆ alkoxy-C₆₋₁₄ aryl group (e.g., methoxyphenyl); a C₁₋₆ alkyl-carbonyl-C₆₋₁₄ aryl group (e.g., acetylphenyl); a heterocyclic group (e.g., thienyl, furyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, indolyl, 1H-indazolyl, benzimidazolyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl) optionally substituted by 1 to 3 substituent(s) selected from oxo, C₁₋₆ alkyl (e.g., methyl, ethyl) and C₁₋₆ alkoxy (e.g., methoxy, ethoxy); a C₆₋₁₄ aryloxy group (e.g., phenoxy); a C₇₋₁₃ aralkyloxy group (e.g., benzyloxy); a C₁₋₆ alkylthio group (e.g., methylthio); a C₆₋₁₄ arylthio group (e.g., phenylthio) optionally substituted by 1 to 3 halogen atom(s); a heterocyclic thio group (e.g., pyrimidinylthio) optionally substituted by C₁₋₆ alkyl; a C₁₋₆ alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl); a heterocyclic carbonyl group (e.g., dihydroindolylcarbonyl); a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl); a C₆₋₁₄ arylsulfonyl group (e.g., phenylsulfonyl); a carbamoyl; a C₁₋₆ alkoxy-carboxamide group (e.g., methoxycarboxamide, ethoxycarboxamide); a sulfamoyl group (e.g., sulfamoyl, acetylsulfamoyl) optionally substituted by C₁₋₆ alkyl-carbonyl; and the like can be mentioned. Of these substituents, a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a hydroxy; a nitro; an amino; a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and the like are preferable.

As the substituted amino group, for example, a mono- or di-C₁₋₁₀ alkylamino (e.g., methylamino, dimethylamino, ethylamino, diethylamino, ethylmethylamino, propylamino, dibutylamino); a mono- or di-C₂₋₁₀ alkenylamino (e.g., diallylamino) [optionally substituted by C₁₋₆ alkoxy-carbonyl]; a mono- or di-C₃₋₁₀ cycloalkylamino (e.g., cyclohexylamino); a mono- or di-C₁₋₁₀ alkyl-carboxamide (e.g., acetylamino, propionylamino) [optionally substituted by 1 to 3 substituent(s) selected from a heterocyclic thio optionally substituted C₁₋₆ alkyl (e.g., pyrimidinylthio), C₆₋₁₄ arylthio optionally substituted by 1 to 3 halogen atom(s), cyano, C₁₋₆ alkylthio, halogen atom, heterocyclic carbonyl (e.g., dihydroindolylcarbonyl)]; a C₆₋₁₄ aryl-carboxamide (e.g., benzoylamino); a C₆₋₁₄ arylamino (e.g., phenylamino); a N-C₁₋₁₀ alkyl-N-C₆₋₁₄ arylamino (e.g., N-methyl-N-phenylamino); a N-C₁₋₁₀ alkyl-N-C₇₋₁₃ aralkylamino (e.g., N-methyl-N-benzylamino); a mono- or di-C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide); a mono- or di-C₆₋₁₄ aryl-carboxamide (e.g., phenylcarboxamide) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkoxy, C₆₋₁₄ aryloxy and a heterocyclic group (e.g., triazolyl, tetrazolyl)]; a mono- or di-C₇₋₁₃ aralkyl-carboxamide (e.g., benzylcarboxamide, phenethylcarboxamide, phenylpropylcarboxamide, phenylbutylcarboxamide) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkoxy and a halogen atom]; an aromatic heterocyclic-carboxamide (e.g., furylcarboxamide, pyrrolylcarboxamide, thienylcarboxamide, pyridylcarboxamide, pyrimidinylcarboxamide, 1H-indazolylcarboxamide, benzofuranylcarboxamide, quinolylcarboxamide) [optionally substituted by 1 to 3 substituent(s) selected from a halogen atom and C₁₋₆

alkyl]; a 5 to 7-membered non-aromatic heterocyclic-carboxamide (e.g., tetrahydrofurylcarboxamide, thiomorpholinocarboxamide, piperidinocarboxamide, piperazinocarboxamide, hexamethyleniminylcarboxamide, thiazolidinylcarboxamide) [optionally substituted by 1 to 3 substituent(s) selected from oxo, C₁₋₆ alkoxy-carbonyl, C₁₋₆ alkoxy-C₆₋₁₄ aryl (e.g., methoxyphenyl), C₁₋₆ alkyl-carbonyl-C₆₋₁₄ aryl (e.g., acetylphenyl), carbamoyl, C₇₋₁₃ aralkyl (e.g., benzyl), heterocyclic group (e.g., piperidino)]; a C₃₋₁₀ cycloalkyl-carboxamide (e.g., cyclopentylcarboxamide, cyclohexylcarboxamide) [optionally substituted by C₁₋₆ alkyl optionally substituted by C₁₋₆ alkoxy-carboxamide (e.g., methoxycarboxamide, ethoxycarboxamide)]; a C₈₋₁₃ arylalkenyl-carboxamide (e.g., styrylcarboxamide) [optionally substituted by a halogen atom]; a C₈₋₁₃ arylalkynyl-carboxamide (e.g., phenylethynylcarboxamide); an aromatic heterocyclic (e.g., thienyl, furyl, indolyl)-C₁₋₆ alkyl-carboxamide; a C₆₋₁₄ arylsulfonylamino (e.g., phenylsulfonylamino); a mono- or di-C₁₋₆ alkyl-carbamoylamino (e.g., methylcarbamoylamino, tert-butylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, halogen atom, C₁₋₆ alkoxy-carbonyl, C₁₋₆ alkoxy-carboxamide, cyano, C₁₋₆ alkylsulfonyl and carbamoyl]; a C₃₋₁₀ cycloalkyl-carbamoylamino (e.g., cyclopropylcarbamoylamino, cyclopentylcarbamoylamino, cyclohexylcarbamoylamino) [optionally substituted by hydroxy]; a C₆₋₁₄ aryl-carbamoylamino (e.g., phenylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkyl optionally substituted by 1 to 3 halogen atom(s), sulfamoyl optionally substituted by C₁₋₆ alkyl-carbonyl, mono- or di-C₁₋₆ alkylamino, mono- or di-C₁₋₁₀ alkylphosphono-C₁₋₆ alkyl group, halogen atom, C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl), C₇₋₁₃ aralkyloxy (e.g., benzyloxy) and C₁₋₆ alkoxy]; a C₇₋₁₄ aralkyl-carbamoylamino (e.g., benzylcarbamoylamino, phenethylcarbamoylamino, diphenylethylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkyl optionally substituted by 1 to 3 substituent(s) selected from mono- or di-C₁₋₆ alkylamino and halogen atom, a halogen atom, a sulfamoyl, a hydroxyl, and C₁₋₆ alkoxy]; a C₁₋₆ alkoxy-carbonylcarbamoylamino (e.g., methoxycarbonylcarbamoylamino, ethoxycarbonylcarbamoylamino); a C₄₋₁₃ cycloalkylalkyl-carbamoylamino (e.g., cyclohexylmethylcarbamoylamino); a heterocyclic (e.g., thienyl, furyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, indolyl, 1H-indazolyl, benzimidazolyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl)-C₁₋₁₀ alkyl-carbamoylamino (e.g., methylcarbamoylamino, ethylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from oxo, C₁₋₆ alkyl, hydroxy and C₁₋₆ alkoxy]; an aromatic heterocyclic carbamoylamino (e.g., isoxazolylcarbamoylamino, benzothiazolylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkyl and C₁₋₆ alkoxy]; a non-aromatic heterocyclic carbamoylamino (e.g., pyrrolidinylcarbamoylamino) [optionally substituted by C₁₋₆ alkyl]; a C₇₋₁₄ aralkyloxy-carbamoylamino (e.g., benzyloxycarbamoylamino); and the like can be mentioned.

As the “optionally substituted hydroxy group”, for example, a hydroxy group optionally substituted by a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkenyl group, a C₆₋₁₄ aryl group, a C₇₋₁₄ aralkyl, a C₁₋₁₅ acyl group or a heteroaryl group, each of which is optionally substituted can be mentioned.

Here, as the C₁₋₁₀ alkyl group, C₂₋₁₀ alkenyl group, C₃₋₁₀ cycloalkyl group, C₃₋₁₀ cycloalkenyl group, C₆₋₁₄ aryl group

and C₇₋₁₄ aralkyl, those exemplified for the “hydrocarbon group” of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

As the C₁₋₁₅ acyl group, those exemplified for the substituent of the aforementioned “optionally substituted amino group” can be mentioned.

As the “heteroaryl group”, for example, aromatic heterocyclic groups exemplified for the substituents of the “optionally substituted heterocyclic group” for R¹ can be mentioned. Of these, pyridyl, imidazolyl, triazolyl, pyrimidinyl and the like are preferable.

These “C₁₋₁₀ alkyl group”, “C₂₋₁₀ alkenyl group”, “C₃₋₁₀ cycloalkyl group”, “C₃₋₁₀ cycloalkenyl group”, “C₆₋₁₄ aryl group”, “C₇₋₁₄ aralkyl”, “C₁₋₁₅ acyl group” and “heteroaryl group” may have 1 or 2 substituent(s) at substitutable position(s). As such substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a hydroxy, a nitro, an amino, a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and the like can be mentioned.

As the substituted hydroxy group, for example, an alkoxy group, an alkenyloxy group, a cycloalkyloxy group, a cycloalkenyloxy group, an aryloxy group, an aralkyloxy group, an acyloxy group, a heteroaryloxy group, each of which is optionally substituted and the like, can be mentioned.

As preferable examples of the alkoxy group, a C₁₋₁₀ alkoxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy and the like, can be mentioned.

As preferable examples of the alkenyloxy group, a C₂₋₁₀ alkenyloxy group, such as allyloxy, crotyloxy, 2-pentenylloxy, 3-hexenyloxy and the like, can be mentioned.

As preferable examples of the cycloalkyloxy group, a C₃₋₁₀ cycloalkyloxy group, such as cyclobutoxy, cyclopentylloxy, cyclohexyloxy and the like, can be mentioned.

As preferable examples of the cycloalkenyloxy group, C₃₋₁₀ cycloalkenyloxy group, such as 2-cyclopentenylloxy, 2-cyclohexenyloxy and the like, can be mentioned.

As preferable examples of the aryloxy group, a C₆₋₁₄ aryloxy group, such as phenoxy, naphthyloxy and the like, can be mentioned.

As preferable examples of the aralkyloxy group, a C₇₋₁₄ aralkyloxy group, such as benzyloxy, phenethylloxy, naphthylmethylloxy and the like, can be mentioned.

As preferable examples of the acyloxy group, a C₂₋₁₃ acyloxy group, such as C₁₋₆ alkyl-carbonyloxy (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy) and the like, can be mentioned.

As preferable examples of the heteroaryloxy group, a 5- to 7-membered monocyclic heteroaryloxy group, such as 2-pyridyloxy, 3-pyridyloxy, 2-imidazolylloxy, 2-pyrimidinylloxy, 1,2,4-triazol-5-yloxy and the like, can be mentioned.

The above-mentioned alkoxy group, alkenyloxy group, cycloalkyloxy group, cycloalkenyloxy group, aryloxy group, aralkyloxy group, acyloxy group and heteroaryloxy group may have 1 or 2 substituent(s) at substitutable position(s). As such substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) option-

ally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a hydroxy, a nitro, an amino, a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl) and the like can be mentioned.

As the optionally substituted thiol group, for example, a thiol group optionally substituted by “C₁₋₁₀ alkyl group”, “C₂₋₁₀ alkenyl group”, “C₃₋₁₀ cycloalkyl group”, “C₃₋₁₀ cycloalkenyl group”, “C₆₋₁₄ aryl group”, “C₇₋₁₄ aralkyl”, “C₁₋₁₅ acyl group” or “heteroaryl group”, each of which is optionally substituted, and the like can be mentioned.

Here, as the “C₁₋₁₀ alkyl group”, “C₂₋₁₀ alkenyl group”, “C₃₋₁₀ cycloalkyl group”, “C₃₋₁₀ cycloalkenyl group”, “C₆₋₁₄ aryl group”, “C₇₋₁₄ aralkyl”, “C₁₋₁₅ acyl group” and “heteroaryl group”, those respectively exemplified for the aforementioned “optionally substituted hydroxy group” can be mentioned. These groups may have 1 or 2 substituent(s) at substitutable position(s). As such substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkyl group (e.g., methyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a hydroxy, a nitro, an amino, a C₁₋₆ alkylsulfonyl group (e.g., methylsulfonyl), an oxo, a pyridyl and the like can be mentioned.

As the substituted thiol group, for example, an alkylthio, an alkenylthio, a cycloalkylthio, a cycloalkenylthio, an arylthio, an aralkylthio, an acylthio, a heteroarylthio, each of which is optionally substituted, and the like, can be mentioned.

As preferable examples of the alkylthio group, a C₁₋₁₀ alkylthio group, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio and the like, can be mentioned.

As preferable examples of the alkenylthio group, a C₂₋₁₀ alkenylthio group, such as allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio and the like can be mentioned.

As preferable examples of the cycloalkylthio group, a C₃₋₁₀ cycloalkylthio group, such as cyclobutylthio, cyclopentylthio, cyclohexylthio and the like, can be mentioned.

As preferable examples of the cycloalkenylthio group, a C₃₋₁₀ cycloalkenylthio group, such as 2-cyclopentenylthio, 2-cyclohexenylthio and the like, can be mentioned.

As preferable examples of the arylthio group, a C₆₋₁₄ arylthio group, such as phenylthio, naphthylthio and the like, can be mentioned.

As preferable examples of the aralkylthio group, a C₇₋₁₄ aralkylthio group, such as benzylthio, phenethylthio, naphthylmethylthio and the like, can be mentioned.

As preferable examples of the acylthio group, a C₂₋₁₃ acylthio group, such as a C₁₋₆ alkyl-carbonylthio group (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio), and the like can be mentioned.

As preferable examples of the heteroarylthio group, a 5- to 7-membered monocyclic heteroarylthio group, such as 2-pyridylthio, 3-pyridylthio, 2-imidazolylthio, 2-pyrimidinylthio, 1,2,4-triazol-5-ylthio, 1,2,4-triazol-3-ylthio and the like, can be mentioned.

The above-mentioned alkylthio group, alkenylthio group, cycloalkylthio group, cycloalkenylthio group, arylthio group, aralkylthio group, acylthio group and heteroarylthio group may have 1 or 2 substituent(s) at substitutable position(s). As such substituent, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkyl (e.g., methyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine),

a C₁₋₆ alkoxy (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a hydroxy, a nitro, an amino, a C₁₋₆ alkylsulfonyl (e.g., methylsulfonyl), an oxo, pyridyl and the like can be mentioned.

As the acyl group of the “optionally substituted acyl group”, for example, a group represented by the formula: —COR³, —CO—OR³, —SO₂R³, —SOR³, —PO₃R³R⁴, —CO—NR^{3a}R^{4a}, —CS—NR^{3a}R^{4a} wherein R³ and R⁴ are the same or different and each is a hydrogen atom, a hydrocarbon group or a heterocyclic group, or R³ and R⁴ may form a heterocycle together with the adjacent oxo-substituted phosphorus atom and 2 oxygen atoms; R^{3a} and R^{4a} are the same or different and each is a hydrogen atom, a hydrocarbon group or a heterocyclic group, or R^{4a} and R^{5a} may form a nitrogen-containing heterocycle together with the adjacent nitrogen atom, and the like can be mentioned.

As the “hydrocarbon group” for R³, R⁴, R^{3a} or R^{4a}, those exemplified for the “hydrocarbon group” of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

The hydrocarbon group is preferably a C₁₋₁₀ alkyl group (preferably methyl, ethyl, propyl, butyl, tert-butyl, pentyl, 1-ethylpropyl, 2,2-dimethylpropyl, isopentyl, hexyl); a C₂₋₁₀ alkenyl group (preferably 1-propenyl); a C₂₋₁₀ alkynyl group (preferably 2-propynyl); a C₃₋₁₀ cycloalkyl group (preferably cyclopropyl, cyclopentyl, cyclohexyl, tetrahydronaphthyl) which may be condensed with a benzene ring; a C₃₋₁₀ cycloalkenyl group (preferably 2-cyclohexenyl); a C₆₋₁₄ aryl group (preferably phenyl, dihydroindenyl, biphenyl) which may be condensed with a C₃₋₁₀ cycloalkane (preferably cyclopentane); a C₇₋₁₄ aralkyl group (preferably benzyl, phenethyl, phenylpropyl, phenylbutyl, naphthylmethyl, benzhydryl, diphenylethyl); a C₈₋₁₃ arylalkenyl group (preferably styryl); a C₈₋₁₃ arylalkynyl group (preferably phenylethynyl); a C₄₋₁₃ cycloalkylalkyl group (preferably cyclohexylmethyl); a C₄₋₁₃ cycloalkenylalkyl group (preferably cyclohexenylmethyl, cyclohexenylethyl) and the like.

As the “heterocyclic group” for R³, R⁴, R^{3a} or R^{4a}, the aromatic heterocyclic group and the non-aromatic heterocyclic group exemplified for the substituents of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

The heterocyclic group is preferably thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, quinolyl, isoquinolyl, pyrrolidinyl, piperidinyl, piperazinyl, furyl, thienyl, pyrimidinyl, benzofuryl, 1H-indazolyl, morpholinyl, thiomorpholinyl, hexamethyleniminyl, tetrahydroisoquinolyl, oxazolidinyl, thiazolidinyl and the like.

As the heterocycle formed by R³ and R⁴ together with the adjacent oxo-substituted phosphorus atom and 2 oxygen atoms, for example, a 4- to 7-membered heterocycle containing an oxo-substituted phosphorus atom and 2 oxygen atoms besides carbon atoms as a ring-constituting atom, which may further contain 1 or 2 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom, and the like can be mentioned. As preferable examples of such heterocycle, 2-oxide-1,3,2-dioxaphosphinane; 2-oxide-1,3,2-dioxaphosphorane and the like can be mentioned.

As the “nitrogen-containing heterocycle” formed by R^{3a} and R^{4a} together with the adjacent nitrogen atom, for example, a 5- to 7-membered nitrogen-containing heterocycle containing at least one nitrogen atom besides carbon atoms as a ring-constituting atom, which may further contain 1 or 2 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom, and the like can be mentioned. As preferable examples of such nitrogen-con-

taining heterocycle, pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine and the like can be mentioned.

Preferable examples of the "acyl group" include formyl; carboxyl; carbamoyl; thiocarbamoyl; C₁₋₁₀ alkyl-carbonyl (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl); C₂₋₁₀ alkenyl-carbonyl (e.g., crotonyl); C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl); C₃₋₁₀ cycloalkenyl-carbonyl (e.g., 2-cyclohexenecarbonyl); C₆₋₁₄ aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl); C₇₋₁₄ aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl, phenylpropylcarbonyl, phenylbutylcarbonyl); C₈₋₁₃ arylalkenyl-carbonyl (e.g., styrylcarbonyl); C₈₋₁₃ arylalkynyl-carbonyl (e.g., phenylethynylcarbonyl); aromatic heterocyclic carbonyl (e.g., nicotinoyl, isonicotinoyl, furylcarbonyl, thienylcarbonyl, pyrimidinylcarbonyl, benzofuranylcarbonyl, 1H-indazolylcarbonyl, quinolylcarbonyl); non-aromatic heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazinocarbonyl, thiazolidinylcarbonyl, hexamethyleniminylcarbonyl, tetrahydroisoquinolylcarbonyl); C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl); C₆₋₁₄ aryloxy-carbonyl (e.g., phenyloxycarbonyl, naphthyloxycarbonyl); C₇₋₁₄ aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethylloxycarbonyl); mono- or di-C₁₋₆ alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl); mono- or di-C₁₋₆ alkyl-thiocarbamoyl (e.g., methylthiocarbamoyl, ethylthiocarbamoyl); C₆₋₁₄ aryl-carbamoyl (e.g., phenylcarbamoyl); C₃₋₁₀ cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl); C₇₋₁₄ aralkyl-carbamoyl (e.g., benzylcarbamoyl, phenethylcarbamoyl, diphenylethylcarbamoyl); C₄₋₁₃ cycloalkylalkyl-carbamoyl (e.g., cyclohexylmethylcarbamoyl); aromatic heterocyclic carbamoyl (e.g., isoxazolylcarbamoyl, benzothiazolylcarbamoyl); non-aromatic heterocyclic carbamoyl (e.g., pyrrolidinylcarbamoyl); C₁₋₁₀ alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl); C₁₋₁₀ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl); C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl); (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (e.g., dimethylphosphono; diethylphosphono; diisopropylphosphono; dibutylphosphono; 2-oxide-1,3,2-dioxaphosphinanyl); mono- or di-(C₁₋₆ alkyl optionally substituted by 1 to 3 halogen(s))-sulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl) and the like can be mentioned.

The acyl group may have 1 to 3 substituent(s) at substitutable position(s). As such substituent, for example, a C₁₋₆ alkyl (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a C₁₋₆ alkoxy (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a nitro; a hydroxy; an amino optionally mono- or di-substituted by C₁₋₆ alkyl (e.g., methyl, ethyl); a cyano; a mono- or di-C₁₋₁₀ alkylphosphono-C₁₋₆ alkyl group (e.g., dimethylphosphonomethyl, diethylphosphonomethyl, dimethylphosphonoethyl); a C₆₋₁₄ aryl (e.g., phenyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), C₁₋₆ alkyl (e.g., methyl, ethyl), C₁₋₆ alkoxy (e.g., methoxy, ethoxy) and C₁₋₆ alkyl-carbonyl (e.g., acetyl); a C₇₋₁₃ aralkyl (e.g., ben-

zyl); a C₁₋₆ alkylthio (e.g., methylthio) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a C₆₋₁₄ aryloxy (e.g., phenoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a C₆₋₁₄ arylthio (e.g., phenylthio) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine); a C₇₋₁₃ aralkyloxy (e.g., benzyloxy); a heterocyclic thio (e.g., pyrimidinylthio) optionally substituted by C₁₋₆ alkyl (e.g., methyl, ethyl); a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl); a C₁₋₆ alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl); a C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl); a carbamoyl; a sulfamoyl optionally substituted by C₁₋₆ alkyl-carbonyl (e.g., acetyl); a heterocyclic carbonyl (e.g., dihydroindolylcarbonyl); a C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide); a C₇₋₁₃ aralkyloxy-carboxamide (e.g., benzyloxycarboxamide) a heterocyclic group (e.g., thienyl, furyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, indolyl, 1H-indazolyl, benzimidazolyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl) optionally substituted by 1 to 3 substituent(s) selected from oxo, C₁₋₆ alkyl (e.g., methyl, ethyl) and C₁₋₆ alkoxy (e.g., methoxy, ethoxy); and the like can be mentioned.

As preferable examples of the "acyl group", formyl; carboxyl; carbamoyl; thiocarbamoyl; C₁₋₁₀ alkyl-carbonyl (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl); C₂₋₁₀ alkenyl-carbonyl (e.g., crotonyl); C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl); C₃₋₁₀ cycloalkenyl-carbonyl (e.g., 2-cyclohexenecarbonyl); C₆₋₁₄ aryl-carbonyl (e.g., benzoyl, 1-naphthoyl, 2-naphthoyl); C₇₋₁₄ aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl, phenylpropylcarbonyl, phenylbutylcarbonyl); C₈₋₁₃ arylalkenyl-carbonyl (e.g., styrylcarbonyl); C₈₋₁₃ arylalkynyl-carbonyl (e.g., phenylethynylcarbonyl); aromatic heterocyclic carbonyl (e.g., nicotinoyl, isonicotinoyl, furylcarbonyl, thienylcarbonyl, pyrimidinylcarbonyl, benzofuranylcarbonyl, 1H-indazolylcarbonyl, quinolylcarbonyl); non-aromatic heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, piperazinocarbonyl, thiazolidinylcarbonyl, hexamethyleniminylcarbonyl, tetrahydroisoquinolylcarbonyl); C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl); C₆₋₁₄ aryloxy-carbonyl (e.g., phenyloxycarbonyl, naphthyloxycarbonyl); C₇₋₁₄ aralkyloxy-carbonyl (e.g., benzyloxycarbonyl, phenethylloxycarbonyl); mono- or di-(C₁₋₆ alkyl optionally having 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkoxy-carbonyl)-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl, trifluoroethylcarbamoyl, butylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl); mono- or di-(C₁₋₆ alkyl optionally substituted by 1 to 3 halogen(s))-thiocarbamoyl (e.g., methylthiocarbamoyl, ethylthiocarbamoyl); C₆₋₁₄ aryl-carbamoyl (e.g., phenylcarbamoyl); C₃₋₁₀ cycloalkyl-carbamoyl (e.g., cyclopropylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl); C₇₋₁₄ aralkyl-carbamoyl (e.g., benzylcarbamoyl, phenethylcarbamoyl, diphenylethylcarbamoyl); C₄₋₁₃ cycloalkylalkyl-carbamoyl (e.g., cyclohexylmethylcarbamoyl); aromatic heterocyclic carbamoyl (e.g., isoxazolylcarbamoyl, benzothiazolylcarbamoyl); non-aromatic heterocyclic carbamoyl (e.g., pyrrolidinylcarbamoyl); C₁₋₁₀ alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl); C₁₋₁₀ alkylsulfonyl group (e.g., methylsulfonyl, ethyl-

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sulfonyl); C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl); (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (e.g., dimethylphosphono; diethylphosphono; diisopropylphosphono; dibutylphosphono; 2-oxide-1,3,2-dioxaphosphinanyl); mono- or di-(C₁₋₆ alkyl optionally substituted by 1 to 3 halogen(s))-sulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl) and the like can be mentioned.

In addition, as the “optionally substituted acyl group”. C₁₋₆ alkoxy-carbamoyl (e.g., methoxycarbamoyl), C₁₋₆ alkoxy-carbonylcarbamoyl (e.g., methoxycarbonylcarbamoyl, ethoxycarbonylcarbamoyl), C₇₋₁₄ aralkyloxy-carbamoyl (e.g., benzyloxycarbamoyl) and the like can be also mentioned.

The “hydrocarbon group” of the “optionally substituted hydrocarbon group” for R¹ is preferably a C₁₋₁₀ alkyl group, a C₆₋₁₄ aryl group, a C₃₋₁₀ cycloalkyl group, a C₇₋₁₄ aralkyl group, a C₈₋₁₃ arylalkenyl group, a C₄₋₁₃ cycloalkylalkyl group and the like. The hydrocarbon group is more preferably a C₆₋₁₄ aryl group, and phenyl, naphthyl and the like are particularly preferable.

The substituent of the “optionally substituted hydrocarbon group” for R¹ is preferably a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a hydroxy, an amino, a C₁₋₃ alkylendioxy (e.g., methylenedioxy, ethylenedioxy) and the like. The number of the substituent is, for example, 1 to 3.

As the “heterocyclic group” of the “optionally substituted heterocyclic group” for R¹, those exemplified for the aforementioned “heterocyclic group” for the aforementioned R³ can be mentioned.

The heterocyclic group is preferably an azolyl group optionally condensed with a benzene ring, such as pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, and the like.

Of these, imidazolyl, benzimidazolyl, indolyl, 1H-indazolyl and the like are preferable, and imidazolyl, benzimidazolyl and the like are particularly preferable.

The heterocyclic group for R¹ may have 1 to 3 substituent(s) at substitutable position(s). As such substituent, for example, an optionally substituted aliphatic hydrocarbon group, an optionally substituted alicyclic hydrocarbon group, an optionally substituted aromatic hydrocarbon group, an optionally substituted aromatic heterocyclic group, an optionally substituted non-aromatic heterocyclic group, a halogen atom, a nitro, an optionally substituted amino group, an optionally substituted acyl group, optionally substituted hydroxy group, an optionally substituted thiol group, an optionally substituted acyl group, a C₁₋₃ alkylendioxy, an oxo and the like can be mentioned.

Here, as the “aliphatic hydrocarbon group”, “alicyclic hydrocarbon group” and “aromatic hydrocarbon group” of the “optionally substituted aliphatic hydrocarbon group”, “optionally substituted alicyclic hydrocarbon group” and “optionally substituted aromatic hydrocarbon group”, those exemplified for the “hydrocarbon group” of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

As the “aromatic heterocyclic group” and “non-aromatic heterocyclic group” of the “optionally substituted aromatic heterocyclic group” and “optionally substituted non-aromatic heterocyclic group”, those exemplified for the substituent of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

Moreover, as the “halogen atom”, “optionally substituted amino group”, “optionally substituted acyl group”, “option-

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ally substituted hydroxy group”, “optionally substituted thiol group”, “optionally substituted acyl group” and “C₁₋₃ alkylendioxy”, those exemplified for the substituent of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

In the aforementioned “optionally substituted aliphatic hydrocarbon group”, as the substituent, for example,

- 1) a hydroxy;
- 2) a cyano;
- 3) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 4) an amidino;
- 5) a carboxyl;
- 6) a sulfo;
- 7) an azide;
- 8) a nitro;
- 9) a nitroso;
- 10) a C₃₋₁₀ cycloalkyl;
- 11) a C₆₋₁₄ aryl (e.g., phenyl, naphthyl);
- 12) a 5- or 6-membered aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl);
- 13) a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl);
- 14) a C₁₋₆ alkoxy optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 15) a C₂₋₆ alkenyloxy optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 16) a C₃₋₁₀ cycloalkyloxy;
- 17) a C₆₋₁₄ aryloxy (e.g., phenyloxy, naphthyloxy);
- 18) a C₇₋₁₃ aralkyloxy;
- 19) a thiol;
- 20) a C₁₋₆ alkylthio optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 21) a C₂₋₆ alkenylthio optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 22) a C₃₋₁₀ cycloalkylthio;
- 23) a C₆₋₁₄ arylthio (e.g., phenylthio, naphthylthio);
- 24) a C₇₋₁₃ aralkylthio;
- 25) a C₁₋₆ alkyl-carbonyl;
- 26) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl);
- 27) a (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono, 2-oxide-1,3,2-dioxaphosphinanyl);
- 28) a carbamoyl (e.g., carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl) optionally mono- or di-substituted by C₁₋₆ alkyl optionally substituted by 1 to 3 halogen(s);
- 29) a sulfamoyl (e.g., sulfamoyl, methylsulfamoyl, ethylsulfamoyl) optionally mono- or di-substituted by C₁₋₆ alkyl optionally substituted by 1 to 3 halogen(s);
- 30) a thiocarbamoyl;
- 31) an amino optionally mono- or di-substituted by substituent selected from C₁₋₆ alkyl and C₁₋₆ alkyl-carbonyl; and the like can be mentioned. The number of substituents is, for example, 1 to 3.

In the aforementioned “optionally substituted alicyclic hydrocarbon group”, “optionally substituted aromatic hydrocarbon group”, “optionally substituted aromatic het-

erocyclic group” and “optionally substituted non-aromatic heterocyclic group”, as the substituent, for example,

- 1) a hydroxy;
- 2) a cyano;
- 3) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 4) an amidino;
- 5) a carboxyl;
- 6) a sulfo;
- 7) an azide;
- 8) a nitro;
- 9) a nitroso;
- 10) a C₁₋₆ alkyl optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 11) a C₂₋₆ alkenyl optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 12) a C₇₋₁₃ aralkyl;
- 13) a C₃₋₁₀ cycloalkyl;
- 14) a C₆₋₁₄ aryl (e.g., phenyl, naphthyl);
- 15) a 5- or 6-membered aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl);
- 16) a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidino, pyrrolidinyl, piperazinyl);
- 17) a C₁₋₆ alkoxy optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 18) a C₂₋₆ alkenyloxy optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 19) a C₃₋₁₀ cycloalkyloxy;
- 20) a C₆₋₁₄ aryloxy (e.g., phenyloxy, naphthyloxy);
- 21) a C₇₋₁₃ aralkyloxy;
- 22) a thiol;
- 23) a C₁₋₆ alkylthio optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 24) a C₂₋₆ alkenylthio optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- 25) a C₃₋₁₀ cycloalkylthio;
- 26) a C₆₋₁₄ arylthio (e.g., phenylthio, naphthylthio);
- 27) a C₇₋₁₃ aralkylthio;
- 28) a C₁₋₆ alkyl-carbonyl;
- 29) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl);
- 30) a (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono, 2-oxide-1,3,2-dioxaphosphinanyl);
- 31) a carbamoyl (e.g., carbamoyl, methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl) optionally mono- or di-substituted by C₁₋₆ alkyl optionally substituted by 1 to 3 halogen(s);
- 32) a sulfamoyl (e.g., sulfamoyl, methylsulfamoyl, ethylsulfamoyl) optionally mono- or di-substituted by C₁₋₆ alkyl optionally substituted by 1 to 3 halogen(s);
- 33) a thiocarbamoyl;
- 34) an amino optionally mono- or di-substituted by substituent selected from C₁₋₆ alkyl and C₁₋₆ alkyl-carbonyl; and the like can be mentioned. The number of substituents is, for example, 1 to 3.

The substituent of the “optionally substituted heterocyclic group” for R¹ preferably includes a C₁₋₆ alkyl (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g.,

methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a hydroxy, an amino, a C₆₋₁₄ aryl (e.g., phenyl), a C₁₋₃ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy), a C₁₋₁₀ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl), a hydroxy-C₁₋₆ alkyl (e.g., hydroxymethyl) and the like. The number of substituents is, for example, 1 to 3.

As the “optionally substituted hydroxy group”, “optionally substituted thiol group” and “optionally substituted amino group” for R¹, those exemplified for the substituent of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

R¹ is preferably an “optionally substituted heterocyclic group”. The heterocyclic group is preferably an azolyl group optionally condensed with a benzene ring (e.g., pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl), and the like. Of these, imidazolyl, benzimidazolyl, indolyl, 1H-indazolyl and the like are preferable, and imidazolyl, benzimidazolyl and the like are particularly preferable.

R¹ is more preferably an “azolyl group optionally condensed with a benzene ring (e.g., pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl)” which is optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a hydroxy, an amino, a C₆₋₁₄ aryl (e.g., phenyl), a C₁₋₃ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy), a C₁₋₁₀ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl) and a hydroxy-C₁₋₆ alkyl (e.g., hydroxymethyl), and the like. Of these, imidazolyl and benzimidazolyl, each of which is optionally substituted by C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), are preferable. R¹ is particularly preferably benzimidazolyl.

A is an “optionally substituted cyclic amino group” or “—NR²—W—D (R² is a hydrogen atom or an alkyl group, W is a bond or a divalent acyclic hydrocarbon group, and D is an optionally substituted cyclic group, an optionally substituted amino group or an optionally substituted acyl group)”.

As the “cyclic amino group” of the “optionally substituted cyclic amino group”, for example, a 5- to 8-membered nitrogen-containing heterocyclic group containing at least one nitrogen atom besides carbon atoms as ring-constituting atoms and optionally further containing 1 or 2 heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom can be mentioned. Preferable examples of the nitrogen-containing heterocyclic group include 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-azepanyl, 1-azocanyl, 3-thiazolidinyl, 3-oxazolidinyl and the like. Of these, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 4-thiomorpholinyl and the like are preferable.

The “cyclic amino group” optionally has 1 to 3 substituent(s) at substitutable position(s). As such substituent, for example,

- 1) an oxo;
- 2) a hydroxy;
- 3) a cyano;
- 4) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

- 5) a C₁₋₆ alkylendioxy (e.g., methylenedioxy, ethylene-dioxy);
- 6) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a hydroxy, a cyano, a C₁₋₆ alkoxy (e.g., methoxy), an amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl, a 5- or 6-membered aromatic heterocyclic group (e.g., thiazolyl) optionally substituted by C₁₋₆ alkyl, a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidinyl, pyrrolidinyl, piperazinyl, dioxothiazolidinyl, dioxooxazolidinyl) optionally substituted by C₁₋₆ alkyl, a carboxamide, an optionally halogenated mono- or di-C₁₋₆ alkyl-carboxamide (e.g., acetylamino, trifluoroacetylamino), and a mono- or di-C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide);
- 7) a C₆₋₁₄ aryl (e.g., phenyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), an optionally halogenated C₁₋₆ alkyl and a C₁₋₆ alkoxy;
- 8) a C₇₋₁₃ aralkyl group (e.g., benzyl, benzhydryl) optionally substituted by C₁₋₆ alkylendioxy;
- 9) a 5- or 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, piperidinyl, pyrimidinyl, pyrrolidinyl) optionally substituted by C₁₋₆ alkyl group;
- 10) an amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl;
- 11) a C₁₋₆ alkyl-carbonyl (e.g., acetyl);
- 12) a C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl, ethylsulfonyl);
- 13) a C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclohexylcarbonyl);
- 14) a C₆₋₁₄ aryl-carbonyl (e.g., benzoyl);
- 15) a C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl);
- 16) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carbonyl (e.g., styrylcarbonyl);
- 17) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl);
- 18) a 5- or 6-membered aromatic heterocyclic-carbonyl (e.g., furoyl, pyrrolylcarbonyl, thenoyl, pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl;
- 19) a 5- or 6-membered non-aromatic heterocyclic-carbonyl (e.g., tetrahydrofuroyl) optionally substituted by C₁₋₆ alkyl;
- 20) a carboxamide;
- 21) a mono- or di-C₁₋₆ alkyl-carboxamide optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine) and a C₁₋₆ alkyl, such as acetylamino, hexanoylamino, trifluoroacetylamino, N-acetyl-N-methylamino and pentafluoropropionylamino;
- 22) a C₃₋₁₀ cycloalkyl-carboxamide (e.g., cyclohexylcarboxamide);
- 23) a C₆₋₁₄ aryl-carboxamide (e.g., phenylcarboxamide) optionally substituted by C₁₋₆ alkylendioxy;
- 24) a C₇₋₁₃ aralkyl-carboxamide (e.g., benzylcarboxamide, phenethylcarboxamide);
- 25) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carboxamide (e.g., styrylcarboxamide);
- 26) a C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide);

- 27) a 5- or 6-membered aromatic heterocyclic-carboxamide (e.g., furylcarboxamide, pyrrolylcarboxamide, thienylcarboxamide, pyridylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- 28) a 5- or 6-membered non-aromatic heterocyclic-carboxamide (e.g., tetrahydrofurylcarboxamide) optionally substituted by C₁₋₆ alkyl; and the like can be mentioned.

The "optionally substituted cyclic amino group" for A is preferably 1-piperidinyl, 1-piperazinyl, 4-morpholinyl or 4-thiomorpholinyl, each optionally having 1 to 3 substituent(s) selected from

- 1) an oxo;
- 2) a hydroxy;
- 3) a cyano;
- 4) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- 5) a C₁₋₆ alkylendioxy (e.g., methylenedioxy, ethylene-dioxy);
- 6) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituent(s) selected from halogen atom (e.g., fluorine, chlorine, bromine, iodine), hydroxy, cyano, C₁₋₆ alkoxy (e.g., methoxy), amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl, 5- or 6-membered aromatic heterocyclic group (e.g., tetrazolyl) optionally substituted by C₁₋₆ alkyl, a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidinyl, pyrrolidinyl, piperazinyl, dioxothiazolidinyl, dioxooxazolidinyl) optionally substituted by C₁₋₆ alkyl, carboxamide, optionally halogenated mono- or di-C₁₋₆ alkyl-carboxamide (e.g., acetylamino, trifluoroacetylamino), and mono- or di-C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide);
- 7) a C₆₋₁₄ aryl (e.g., phenyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), an optionally halogenated C₁₋₆ alkyl and a C₁₋₆ alkoxy;
- 8) a C₇₋₁₃ aralkyl group (e.g., benzyl, benzhydryl) optionally substituted by C₁₋₆ alkylendioxy;
- 9) a 5- or 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, piperidinyl, pyrimidinyl, pyrrolidinyl) optionally substituted by C₁₋₆ alkyl group;
- 10) an amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl;
- 11) a C₁₋₆ alkyl-carbonyl (e.g., acetyl);
- 12) a C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl, ethylsulfonyl);
- 13) a C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclohexylcarbonyl);
- 14) a C₆₋₁₄ aryl-carbonyl (e.g., benzoyl);
- 15) a C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl);
- 16) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carbonyl (e.g., styrylcarbonyl);
- 17) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl);
- 18) a 5- or 6-membered aromatic heterocyclic-carbonyl (e.g., furoyl, pyrrolylcarbonyl, thenoyl, pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl;
- 19) a 5- or 6-membered non-aromatic heterocyclic-carbonyl (e.g., tetrahydrofuroyl) optionally substituted by C₁₋₆ alkyl;
- 20) a carboxamide;

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- 21) a mono- or di-C₁₋₆ alkyl-carboxamide optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine) and a C₁₋₆ alkyl, such as acetylamino, hexanoylamino, trifluoroacetylamino, N-acetyl-N-methylamino and pentafluoropropionylamino;
- 22) a C₃₋₁₀ cycloalkyl-carboxamide (e.g., cyclohexylcarboxamide);
- 23) a C₆₋₁₄ aryl-carboxamide (e.g., phenylcarboxamide) optionally substituted by C₁₋₆ alkylendioxy;
- 24) a C₇₋₁₃ aralkyl-carboxamide (e.g., benzylcarboxamide, phenethylcarboxamide);
- 25) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carboxamide (e.g., styrylcarboxamide);
- 26) a C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide);
- 27) a 5- or 6-membered aromatic heterocyclic-carboxamide (e.g., furylcarboxamide, pyrrolylcarboxamide, thienylcarboxamide, pyridylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- 28) a 5- or 6-membered non-aromatic heterocyclic-carboxamide (e.g., tetrahydrofurylcarboxamide) optionally substituted by C₁₋₆ alkyl.

As the alkyl group for R², for example, a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl) can be mentioned. Particularly, methyl is preferable. R² is preferably a hydrogen atom.

The “divalent acyclic hydrocarbon group” for W may be straight-chain or branched and saturated or unsaturated, as long as it is an acyclic divalent hydrocarbon group.

As the “divalent acyclic hydrocarbon group”, for example, a “divalent aliphatic hydrocarbon group” can be mentioned. Particularly, a divalent C₁₋₈ aliphatic hydrocarbon group is preferable.

Preferable examples of the “divalent acyclic hydrocarbon group” include:

- (1) a C₁₋₈ alkylene (e.g., —CH₂—, —(CH₂)₂—, —(CH₂)₃—, —(CH₂)₄—, —(CH₂)₅—, —(CH₂)₆—, —(CH₂)₇—, —(CH₂)₈—, —CH(CH₃)—, —C(CH₃)₂—, —(CH(CH₃))₂—, —(CH₂)₂C(CH₃)₂—, —(CH₂)₃C(CH₃)₂— and the like);
- (2) a C₂₋₈ alkenylene (e.g., —CH=CH—, —CH₂—CH=CH—, —C(CH₃)₂—CH=CH—, —CH₂—CH=CH—CH₂—, —CH₂—CH₂—CH=CH—, —CH=CH—CH=CH—, —CH=CH—CH₂—CH₂— and the like) and the like.

The “divalent acyclic hydrocarbon group” is preferably a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms, and is more preferably a C₁₋₄ alkylene. Particularly, —CH₂—, —(CH₂)₂—, —(CH₂)₃—, —(CH₂)₄— and the like are preferable, and specifically, —(CH₂)₂—, —(CH₂)₃—, —(CH₂)₄— and the like are preferable.

W is preferably a bond or a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms and is more preferably a bond or a C₁₋₄ alkylene. Particularly, a bond, —CH₂—, —(CH₂)₂—, —(CH₂)₃—, —(CH₂)₄— and the like are preferable, and specifically, a bond, —(CH₂)₂—, —(CH₂)₃—, —(CH₂)₄— and the like are preferable.

As the “cyclic group” of the “optionally substituted cyclic group” for D is, for example, an alicyclic hydrocarbon group, an aromatic hydrocarbon group, an aromatic heterocyclic group, a non-aromatic heterocyclic group and the like can be mentioned.

Here, as the “alicyclic hydrocarbon group” and “aromatic hydrocarbon group”, those exemplified for the “hydrocarbon group” of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

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As the “aromatic heterocyclic group” and “non-aromatic heterocyclic group”, those exemplified for the substituents of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

The cyclic group is preferably a C₆₋₁₄ aryl group (preferably phenyl, biphenyl), a C₃₋₁₀ cycloalkyl group (preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), a C₃₋₁₀ cycloalkenyl group (preferably cyclohexenyl), a 5- or 6-membered aromatic heterocyclic group optionally condensed with a benzene ring (preferably furyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, indolyl, quinolyl, isoquinolyl, benzothiazolyl, benzothiadiazolyl, isoxazolyl), a 5- or 6-membered non-aromatic heterocyclic group optionally condensed with a benzene ring (preferably pyrrolidinyl, tetrahydrofuranlyl, thiazolinyl, oxazolinyl, thiazolidinyl, oxazolidinyl, dioxolanlyl, piperidinyl, piperazinyl, morpholino, thiomorpholino, dihydrobenzofuranlyl) and the like. The cyclic group is more preferably a C₆₋₁₄ aryl group, and phenyl is particularly preferable.

The “cyclic group” for D may have 1 to 3 substituent(s) at the substitutable position(s). As such substituent, for example,

- (1) an oxo;
- (2) a hydroxy;
- (3) a cyano;
- (4) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
- (5) a C₁₋₆ alkylendioxy (e.g., methylenedioxy, ethylenedioxy);
- (6) a carboxyl;
- (7) a C₁₋₆ alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a hydroxyl; a cyano; a C₁₋₆ alkoxy (e.g., methoxy); an amino optionally mono- or di-substituted by C₁₋₆ alkyl, such as amino, methylamino, dimethylamino; a 5- or 6-membered aromatic heterocyclic group (e.g., thiazolyl) optionally substituted by C₁₋₆ alkyl; a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidinyl, pyrrolidinyl, piperazinyl, dioxothiazolidinyl, dioxooxazolidinyl) optionally substituted by C₁₋₆ alkyl; carboxyl group; C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl); a (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (e.g., dimethylphosphono, diethylphosphono, diisopropylphosphono, dibutylphosphono, 2-oxide-1,3,2-dioxaphosphinanyl); a carbamoyl; a mono- or di-C₁₋₆ alkyl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a hydroxy and a C₁₋₆ alkoxy-carbonyl, such as methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, propylcarbamoyl, trifluoroethylcarbamoyl, methoxycarbonyl ethylcarbamoyl, 2-hydroxy-1-methoxycarbonyl-ethylcarbamoyl and 2-hydroxy-1-methoxycarbonyl-propylcarbamoyl; a mono- or di-C₆₋₁₄ aryl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from an optionally halogenated C₁₋₆ alkyl and a C₁₋₆ alkoxy, such as phenylcarbamoyl, methoxyphenylcarbamoyl and trifluoromethylphenylcarbamoyl; a mono- or di-C₇₋₁₃ aralkyl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from an amino optionally mono- or di-substituted by C₁₋₆ alkyl, an optionally haloge-

- nated C₁₋₆ alkyl, a hydroxy and a C₁₋₆ alkoxy-carbonyl, such as benzylcarbamoyl, phenethylcarbamoyl, dimethylaminobenzylcarbamoyl, methoxycarbonylphenethylcarbamoyl and trifluoromethylbenzylcarbamoyl; a sulfamoyl; and an optionally halogenated mono- or di-C₁₋₆ alkylsulfamoyl (e.g., methylsulfamoyl, ethylsulfamoyl);
- (8) a C₃₋₁₀ cycloalkyl group (e.g., cyclohexyl);
- (9) a C₆₋₁₄ aryl (e.g., phenyl);
- (10) a C₇₋₁₃ aralkyl (e.g., benzyl);
- (11) a 5- or 6-membered aromatic heterocyclic group (e.g., thiadiazolyl);
- (12) a C₁₋₆ alkoxy group, (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- (13) a C₁₋₆ alkylthio (e.g., methylthio) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine);
- (14) a C₆₋₁₄ aryloxy (e.g., phenoxy);
- (15) an amino optionally mono- or di-substituted by C₁₋₆ alkyl, such as amino, methylamino, dimethylamino, ethylamino, diethylamino, ethylmethylamino, propylamino and dibutylamino;
- (16) a phosphono-C₁₋₆ alkylamino optionally mono- or di-substituted by C₁₋₁₀ alkyl, such as phosphonomethylamino and diethylphosphonomethylamino;
- (17) a mono- or di-C₁₋₆ alkyl-carboxamide optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine) and a C₁₋₆ alkyl, such as acetylamino, hexanoylamino, trifluoroacetylamino, N-acetyl-N-methylamino and pentafluoropropionylamino;
- (18) a (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (e.g., dimethylphosphono; diethylphosphono; diisopropylphosphono; dibutylphosphono; 2-oxide-1,3,2-dioxaphosphinanyl);
- (19) a C₁₋₆ alkyl-carbonyl (e.g., acetyl);
- (20) a C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl and ethylsulfonyl);
- (21) a C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclohexylcarbonyl);
- (22) a C₆₋₁₄ aryl-carbonyl (e.g., benzoyl);
- (23) a C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl and phenethylcarbonyl);
- (24) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carbonyl (e.g., styrylcarbonyl);
- (25) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl and tert-butoxycarbonyl);
- (26) a 5- or 6-membered aromatic heterocyclic-carbonyl (e.g., furoyl, pyrrolylcarbonyl and pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl;
- (27) a 5- or 6-membered non-aromatic heterocyclic-carbonyl (e.g., tetrahydrofuroyl) optionally substituted by C₁₋₆ alkyl;
- (28) a carbamoyl optionally mono- or di-substituted by C₁₋₆ alkyl, such as carbamoyl and dimethylcarbamoyl;
- (29) a sulfamoyl optionally mono- or di-substituted by C₁₋₆ alkyl, such as sulfamoyl and dimethylsulfamoyl; and the like can be mentioned.

As the “optionally substituted amino group” and “optionally substituted acyl group” for D, those exemplified for the substituents of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

As preferable examples of the “optionally substituted amino group” for D,

- 1) an amino optionally mono- or di-substituted by substituents selected from a C₁₋₆ alkyl optionally substi-

- tuted by hydroxy, a C₆₋₁₄ aryl, and a 5- or 6-membered aromatic heterocyclic group (e.g., pyridyl) optionally substituted by nitro, such as amino, methylamino, dimethylamino, diisopropylamino, phenylamino and N-phenyl-N-methylamino;
- 2) a mono- or di-C₁₋₆ alkyl-carboxamide optionally substituted by 1 to 3 substituent(s) selected from halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine) and a C₁₋₆ alkyl, such as acetylamino, hexanoylamino, trifluoroacetylamino, N-acetyl-N-methylamino and pentafluoropropionylamino;
- 3) a C₁₋₆ alkoxy-carboxamide optionally substituted by C₁₋₆ alkyl, such as tert-butoxycarboxamide and N-tert-butoxycarbonyl-N-methylamino;
- 4) a C₆₋₁₄ aryl-carboxamide (e.g., phenylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- 5) a C₇₋₁₃ aralkyl-carboxamide (e.g., benzylcarboxamide and phenethylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- 6) a 5- or 6-membered aromatic heterocyclic-carboxamide (e.g., furylcarboxamide, pyrrolylcarboxamide, thienylcarboxamide, pyridylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- 7) a 5- or 6-membered non-aromatic heterocyclic-carboxamide (e.g., tetrahydrofurylcarboxamide) optionally substituted by C₁₋₆ alkyl; and the like can be mentioned.

As preferable examples of the “optionally substituted acyl group” for D,

- (1) a carboxyl;
- (2) a C₁₋₆ alkyl-carbonyl (e.g., acetyl);
- (3) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl);
- (4) a C₁₋₆ alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl);
- (5) a carbamoyl optionally mono- or di-substituted by C₁₋₆ alkyl, such as carbamoyl and dimethylcarbamoyl;
- (6) a sulfamoyl optionally mono- or di-substituted by C₁₋₆ alkyl, such as sulfamoyl and dimethylsulfamoyl;
- (7) a mono- or di-C₆₋₁₄ aryl-carbamoyl (e.g., phenylcarbamoyl);
- (8) a mono- or di-C₇₋₁₃ aralkyl-carbamoyl (e.g., benzylcarbamoyl);
- (9) a (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (e.g., dimethylphosphono; diethylphosphono; diisopropylphosphono; dibutylphosphono; 2-oxide-1,3,2-dioxaphosphinanyl; and the like can be mentioned.

D is preferably an optionally substituted cyclic group, and more preferably “a C₆₋₁₄ aryl group (preferably phenyl, biphenyl)”, “a 5- or 6-membered aromatic heterocyclic group optionally condensed with a benzene ring (preferably furyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, indolyl, quinolyl, isoquinolyl, benzothiazolyl, benzothiadiazolyl, isoxazolyl)” or “a 5- or 6-membered non-aromatic heterocyclic group optionally condensed with a benzene ring (preferably pyrrolidinyl, tetrahydrofuranlyl, thiazolinyl, oxazolinyl, thiazolidinyl, oxazolidinyl, dioxolanlyl, piperidinyl, piperazinyl, morpholino, thiomorpholino, dihydrobenzofuranlyl)”, each of which is optionally substituted by 1 to 3 substituent(s) selected from

- (1) an oxo;
- (2) a hydroxy;
- (3) a cyano;
- (4) a halogen atom;
- (5) a C₁₋₆ alkylendioxy;
- (6) a carboxyl;

- (7) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom; a hydroxy; a cyano; a C₁₋₆ alkoxy; an amino optionally mono- or di-substituted by C₁₋₆ alkyl; a 5- or 6-membered aromatic heterocyclic group (e.g., tetrazolyl) optionally substituted by C₁₋₆ alkyl; a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidinyl, pyrrolidinyl, piperazinyl, dioxothiazolidinyl, dioxooxazolidinyl) optionally substituted by C₁₋₆ alkyl; a carboxyl group; a C₁₋₆ alkoxy-carbonyl; a (mono- or di-C₁₋₁₀ alkyl) phosphono group optionally forming a ring; a carbamoyl; a mono- or di-C₁₋₆ alkyl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, a hydroxy and a C₁₋₆ alkoxy-carbonyl; a mono- or di-C₆₋₁₄ aryl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from an optionally halogenated C₁₋₆ alkyl and a C₁₋₆ alkoxy; a mono- or di-C₇₋₁₃ aralkyl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from an amino optionally mono- or di-substituted by C₁₋₆ alkyl, an optionally halogenated C₁₋₆ alkyl, a hydroxy and a C₁₋₆ alkoxy-carbonyl; a sulfamoyl; and an optionally halogenated mono- or di-C₁₋₆ alkylsulfamoyl;
- (8) a C₃₋₁₀ cycloalkyl group;
- (9) a C₆₋₁₄ aryl;
- (10) a C₇₋₁₃ aralkyl;
- (11) a 5- or 6-membered aromatic heterocyclic group (e.g., thiadiazolyl);
- (12) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atom(s);
- (13) a C₁₋₆ alkylthio optionally substituted by 1 to 3 halogen atom(s);
- (14) a C₆₋₁₄ aryloxy;
- (15) an amino optionally mono- or di-substituted by C₁₋₆ alkyl;
- (16) a phosphono-C₁₋₆ alkylamino optionally mono- or di-substituted by C₁₋₁₀ alkyl;
- (17) a mono- or di-C₁₋₆ alkyl-carboxamide optionally substituted by 1 to 3 substituent(s) selected from a halogen atom and a C₁₋₆ alkyl;
- (18) a (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring;
- (19) a C₁₋₆ alkyl-carbonyl;
- (20) a C₁₋₆ alkyl-sulfonyl;
- (21) a C₃₋₁₀ cycloalkyl-carbonyl;
- (22) a C₆₋₁₄ aryl-carbonyl;
- (23) a C₇₋₁₃ aralkyl-carbonyl;
- (24) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carbonyl;
- (25) a C₁₋₆ alkoxy-carbonyl;
- (26) a 5- or 6-membered aromatic heterocyclic-carbonyl (e.g., furoyl, pyrrolylcarbonyl and pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl;
- (27) a 5- or 6-membered non-aromatic heterocyclic-carbonyl (e.g., tetrahydrofuroyl) optionally substituted by C₁₋₆ alkyl;
- (28) a carbamoyl optionally mono- or di-substituted by C₁₋₆ alkyl; and
- (29) a sulfamoyl optionally mono- or di-substituted by C₁₋₆ alkyl.

D is particularly preferably a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by C₁₋₆ alkyl group (preferably methyl, ethyl) optionally substituted by (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (preferably dimethylphosphono; diethylphosphono; diisopropylphosphono; dibutylphosphono; 2-oxide-1,3,2-dioxaphosphinanyl).

As the “optionally substituted hydrocarbon group” and “optionally substituted heterocyclic group” for B, those exemplified for R¹ can be mentioned.

B is preferably an “optionally substituted hydrocarbon group”, and is more preferably a C₁₋₁₀ alkyl group (e.g., methyl, isopropyl, t-butyl) or an optionally substituted C₆₋₁₄ aryl group. Particularly, an optionally substituted C₆₋₁₄ aryl group is preferable.

Preferable examples of B include a C₆₋₁₄ aryl group (preferably phenyl or biphenyl, more preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl (e.g., methyl, ethyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g., methoxy, ethoxy, trifluoromethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a formyl, a C₁₋₃ alkylendioxy (e.g., methylenedioxy) and an aromatic heterocyclic group (e.g., benzofuryl).

Particularly, a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., chlorine, bromine) is preferable.

X is an oxygen atom, a sulfur atom or an optionally substituted nitrogen atom.

As the optionally substituted nitrogen atom for X, for example, —NR⁵— wherein R⁵ is a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group or an optionally substituted acyl group, and the like can be mentioned.

Here, as the “optionally substituted hydrocarbon group” and “optionally substituted heterocyclic group” for R⁵, those exemplified for R¹ can be mentioned.

As the optionally substituted acyl group for R⁵, those exemplified for the substituent of the “optionally substituted hydrocarbon group” for R¹ can be mentioned.

R⁵ is preferably a hydrogen atom, an optionally substituted hydrocarbon group and the like, more preferably a hydrogen atom, an optionally substituted alkyl group and the like, and particularly, a hydrogen atom, a C₁₋₄ alkyl group and the like are preferable.

X is preferably an oxygen atom or a sulfur atom, more preferably an oxygen atom.

As the “divalent acyclic hydrocarbon group” for Y, those exemplified for the aforementioned W can be mentioned.

Y is preferably a divalent acyclic hydrocarbon group, more preferably a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms, particularly preferably a C₁₋₄ alkylene (preferably —CH₂—, —(CH₂)₂—, —(CH₂)₃—, —(CH₂)₄—). Of these, —(CH₂)₂—, —(CH₂)₃—, —(CH₂)₄— and the like are preferable, particularly, —(CH₂)₂— and the like are preferable.

As the preferable examples of the compounds represented by the formula (I), the following compounds (A)–(F) and the like can be mentioned.

Compound (A)

A compound wherein

R¹ is an “azolyl group optionally condensed with a benzene ring (e.g., pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl)” optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl optionally substituted by 1 to 3 halogen atom(s), a C₁₋₆ alkoxy optionally substituted by 1 to 3 halogen atom(s), a halogen atom, a nitro, a hydroxy, an amino, a C₆₋₁₄ aryl and a C₁₋₃ alkylendioxy;

A is an optionally substituted cyclic amino group;
 B is a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl optionally substituted by 1 to 3 halogen atom(s), a C₁₋₆ alkoxy, a halogen atom, nitro, formyl and a C₁₋₃ 5
 alkylenedioxy;
 X is an oxygen atom or a sulfur atom; and
 Y is a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms (preferably C₁₋₄ alkylene).

Compound (B)

A compound wherein

R¹ is an "azolyl group optionally condensed with a benzene ring (e.g., pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl)" optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ 15
 alkyl optionally substituted by 1 to 3 halogen atom(s), a C₁₋₆ alkoxy optionally substituted by 1 to 3 halogen atom(s), a halogen atom, a nitro, a hydroxy, an amino, a C₆₋₁₄ aryl and a C₁₋₃ alkylenedioxy;

A is —NR²—W—D wherein R² is a hydrogen atom or a C₁₋₆ alkyl group, W is a bond or C₁₋₄ alkylene, and D is an optionally substituted cyclic group;

B is a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ 25
 alkyl optionally substituted by 1 to 3 halogen atom(s), a C₁₋₆ alkoxy, a halogen atom, nitro, formyl and a C₁₋₃ alkylenedioxy;

X is an oxygen atom or a sulfur atom; and

Y is a divalent aliphatic hydrocarbon group having 1 to 4 30
 carbon atoms (preferably C₁₋₄ alkylene).

Compound (C)

A compound wherein

R¹ is (1) imidazolyl, benzimidazolyl, indolyl or 1H-indazolyl, each of which is optionally substituted by 1 to 3 35
 substituent(s) selected from a C₁₋₆ alkyl (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 40
 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a hydroxy, an amino, a C₆₋₁₄ aryl (e.g., phenyl), a C₁₋₃ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy), a C₁₋₁₀ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl) and a hydroxy-C₁₋₆ 45
 alkyl (e.g., hydroxymethyl); or

(2) a C₁₋₁₀ alkyl group, a C₆₋₁₄ aryl group, a C₃₋₁₀ cycloalkyl group, a C₇₋₁₄ aralkyl group, a C₈₋₁₃ arylalkenyl group, a C₄₋₁₃ cycloalkylalkyl group (preferably a C₆₋₁₄ aryl group), each of which is optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ 50
 alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a hydroxy, an amino, a C₁₋₃ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy);

[R¹ is preferably imidazolyl or benzimidazolyl, each of which is optionally substituted by a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atom(s); more preferably benzimidazolyl];

A is 1-piperidinyl, 1-piperazinyl, 4-morpholinyl or 4-thiomorpholinyl, each optionally having 1 to 3 55
 substituent(s) selected from

1) an oxo;

2) a hydroxy;

3) a cyano;

4) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);

5) a C₁₋₆ alkylenedioxy (e.g., methylenedioxy, ethylenedioxy);

6) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine); a hydroxy; a cyano; a C₁₋₆ alkoxy (e.g., methoxy); amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl; a 5- or 6-membered aromatic heterocyclic group (e.g., tetrazolyl) optionally substituted by C₁₋₆ alkyl; a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidinyl, pyrrolidinyl, piperazinyl, dioxothiazolidinyl, dioxooxazolidinyl) optionally substituted by C₁₋₆ alkyl; a carboxamide; an optionally halogenated mono- or di-C₁₋₆ alkyl-carboxamide (e.g., acetylamino, trifluoroacetylamino); and a mono- or di-C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide);

7) a C₆₋₁₄ aryl (e.g., phenyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), optionally halogenated C₁₋₆ alkyl and C₁₋₆ alkoxy;

8) a C₇₋₁₃ aralkyl group (e.g., benzyl, benzhydryl) optionally substituted by C₁₋₆ alkylenedioxy;

9) a 5- or 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, piperidinyl, pyrimidinyl, pyrrolidinyl) optionally substituted by C₁₋₆ alkyl group;

10) an amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl;

11) a C₁₋₆ alkyl-carbonyl (e.g., acetyl);

12) a C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl, ethylsulfonyl);

13) a C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclohexylcarbonyl);

14) a C₆₋₁₄ aryl-carbonyl (e.g., benzoyl);

15) a C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl);

16) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carbonyl (e.g., styrylcarbonyl);

17) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl);

18) a 5- or 6-membered aromatic heterocyclic-carbonyl (e.g., furoyl, pyrrolylcarbonyl, thenoyl, pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl;

19) a 5- or 6-membered non-aromatic heterocyclic-carbonyl (e.g., tetrahydrofuroyl) optionally substituted by C₁₋₆ alkyl;

20) a carboxamide;

21) a mono- or di-C₁₋₆ alkyl-carboxamide (e.g., acetylamino, hexanoylamino, trifluoroacetylamino, N-acetyl-N-methylamino, pentafluoropropionylamino) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine) and C₁₋₆ alkyl;

22) a C₃₋₁₀ cycloalkyl-carboxamide (e.g., cyclohexylcarboxamide);

23) a C₆₋₁₄ aryl-carboxamide (e.g., phenylcarboxamide) optionally substituted by C₁₋₆ alkylenedioxy;

24) a C₇₋₁₃ aralkyl-carboxamide (e.g., benzylcarboxamide, phenethylcarboxamide);

25) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carboxamide (e.g., styrylcarboxamide);

- 26) a C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide);
- 27) a 5- or 6-membered aromatic heterocyclic-carboxamide (e.g., furylcarboxamide, pyrrolylcarboxamide, thienylcarboxamide, pyridylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- 28) a 5- or 6-membered non-aromatic heterocyclic-carboxamide (e.g., tetrahydrofurylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- B is (1) a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl (e.g., methyl, ethyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g. methoxy, ethoxy, trifluoromethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a formyl, a C₁₋₃ alkylendioxy (e.g., methylenedioxy), an aromatic heterocyclic group (e.g., benzofuryl) or (2) a C₁₋₁₀ alkyl group (e.g., methyl, isopropyl, t-butyl);
- [B is preferably a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 halogen atom(s)(preferably chlorine, bromine)];
- X is an oxygen atom or a sulfur atom; and
- Y is a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms (preferably C₁₋₄ alkylene).

Compound (D)

A compound wherein

- R¹ is (1) imidazolyl, benzimidazolyl, indolyl or 1H-indazolyl, each of which is optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl (e.g., methyl, ethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a hydroxy, an amino, a C₆₋₁₄ aryl (e.g., phenyl), a C₁₋₃ alkylendioxy (e.g., methylenedioxy, ethylenedioxy), a C₁₋₁₀ alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl) and a hydroxy-C₁₋₆ alkyl (e.g., hydroxymethyl); or
- (2) a C₁₋₁₀ alkyl group, a C₆₋₁₄ aryl group, a C₃₋₁₀ cycloalkyl group, a C₇₋₁₄ aralkyl group, a C₈₋₁₃ aralkenyl group, a C₄₋₁₃ cycloalkylalkyl group (preferably a C₆₋₁₄ aryl group), each of which is optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkoxy group (e.g., methoxy, ethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a hydroxy, an amino and a C₁₋₃ alkylendioxy (e.g., methylenedioxy, ethylenedioxy);
- [R¹ is preferably imidazolyl or benzimidazolyl, each of which is optionally substituted by a C₁₋₆ alkyl group optionally substituted by 1 to 3 halogen atom(s); more preferably benzimidazolyl];
- A is —NR²—W—D;
- R² is a hydrogen atom or a C₁₋₆ alkyl group, W is a bond or a C₁₋₄ alkylene, D is “a C₆₋₁₄ aryl group (preferably phenyl, biphenyl)”, “a 5- or 6-membered aromatic heterocyclic group optionally condensed with a benzene ring (preferably furyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, indolyl, quinolyl, isoquinolyl, benzothiazolyl, benzothiadiazolyl, isoxazolyl)” or “a 5- or 6-membered non-aromatic hetero-

- cyclic group optionally condensed with a benzene ring (preferably pyrrolidinyl, tetrahydrofuryl, thiazolyl, oxazolyl, thiazolidinyl, oxazolidinyl, dioxolanyl, piperidinyl, piperazinyl, morpholino, thiomorpholino, dihydrobenzofuryl)”, each of which is optionally substituted by 1 to 3 substituent(s) selected from
- (1) an oxo;
 - (2) a hydroxy;
 - (3) a cyano;
 - (4) a halogen atom;
 - (5) a C₁₋₆ alkylendioxy;
 - (6) a carboxyl;
 - (7) a C₁₋₆ alkyl group optionally substituted by 1 to 3 substituent(s) selected from a halogen atom; a hydroxy; a cyano; a C₁₋₆ alkoxy; an amino optionally mono- or di-substituted by C₁₋₆ alkyl; a 5- or 6-membered aromatic heterocyclic group (e.g., tetrazolyl) optionally substituted by C₁₋₆ alkyl; a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidinyl, pyrrolidinyl, piperazinyl, dioxothiazolidinyl, dioxooxazolidinyl) optionally substituted by C₁₋₆ alkyl; a carboxyl group; a C₁₋₆ alkoxy-carbonyl; a (mono- or di-C₁₋₁₀ alkyl) phosphono group optionally forming a ring; a carbamoyl; a mono- or di-C₁₋₆alkyl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from a halogen atom, hydroxy and C₁₋₆ alkoxy-carbonyl; a mono- or di-C₆₋₁₄ aryl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from optionally halogenated C₁₋₆ alkyl and C₁₋₆ alkoxy; a mono- or di-C₇₋₁₃ aralkyl-carbamoyl optionally substituted by 1 to 3 substituent(s) selected from amino optionally mono- or di-substituted by C₁₋₆ alkyl, optionally halogenated C₁₋₆ alkyl, hydroxy and C₁₋₆ alkoxy-carbonyl; a sulfamoyl; an optionally halogenated mono- or di-C₁₋₆ alkylsulfamoyl;
 - (8) a C₃₋₁₀ cycloalkyl group;
 - (9) a C₆₋₁₄ aryl;
 - (10) a C₇₋₁₃ aralkyl;
 - (11) a 5- or 6-membered aromatic heterocyclic group (e.g., thiadiazolyl);
 - (12) a C₁₋₆ alkoxy group optionally substituted by 1 to 3 halogen atom(s);
 - (13) a C₁₋₆ alkylthio optionally substituted by 1 to 3 halogen atom(s)
 - (14) a C₆₋₁₄ aryloxy;
 - (15) an amino optionally mono- or di-substituted by C₁₋₆ alkyl;
 - (16) a phosphono-C₁₋₆ alkylamino optionally mono- or di-substituted by C₁₋₁₀ alkyl;
 - (17) a mono- or di-C₁₋₆ alkyl-carboxamide optionally substituted by 1 to 3 substituent(s) selected from a halogen atom and C₁₋₆ alkyl;
 - (18) a (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring;
 - (19) a C₁₋₆ alkyl-carbonyl;
 - (20) a C₁₋₆ alkyl-sulfonyl;
 - (21) a C₃₋₁₀ cycloalkyl-carbonyl;
 - (22) a C₆₋₁₄ aryl-carbonyl;
 - (23) a C₇₋₁₃ aralkyl-carbonyl;
 - (24) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carbonyl;
 - (25) a C₁₋₆ alkoxy-carbonyl;
 - (26) a 5- or 6-membered aromatic heterocyclic-carbonyl (e.g., furoyl, pyrrolylcarbonyl, pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl;

- (27) a 5- or 6-membered non-aromatic heterocyclic-carbonyl (e.g., tetrahydrofuroyl) optionally substituted by C₁₋₆ alkyl;
- (28) a carbamoyl optionally mono- or di-substituted by C₁₋₆ alkyl;
- (29) a sulfamoyl optionally mono- or di-substituted by C₁₋₆ alkyl;
- [D is preferably a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by C₁₋₆ alkyl group (preferably methyl, ethyl) optionally substituted by (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (preferably dimethylphosphono; diethylphosphono; diisopropylphosphono; dibutylphosphono; and 2-oxide-1,3,2-dioxaphosphinanyl)];
- B is (1) a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl (e.g., methyl, ethyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g., methoxy, ethoxy, trifluoromethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a formyl, a C₁₋₃ alkylenedioxy (e.g., methylenedioxy), an aromatic heterocyclic group (e.g., benzofuryl) or (2) a C₁₋₁₀ alkyl group (e.g., methyl, isopropyl, t-butyl);
- [B is preferably a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 halogen atom(s) (preferably chlorine, bromine)];
- X is an oxygen atom or a sulfur atom; and
- Y is a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms (preferably C₁₋₄ alkylene)

Compound (E)

A compound wherein

- R¹ is a mono- or di-C₁₋₁₀ alkylamino (e.g., methylamino, dimethylamino, ethylamino, diethylamino, ethylmethylamino, propylamino, dibutylamino); a mono- or di-C₂₋₁₀ alkenylamino (e.g., diallylamino) [optionally substituted by C₁₋₆ alkoxy-carbonyl]; a mono- or di-C₃₋₁₀ cycloalkylamino (e.g., cyclohexylamino); a mono- or di-C₁₋₁₀ alkyl-carboxamide (e.g., acetylamino, propionylamino) [optionally substituted by 1 to 3 substituent(s) selected from heterocyclic thio (e.g., pyrimidinylthio) optionally substituted by C₁₋₆ alkyl, C₆₋₁₄ arylthio optionally substituted by 1 to 3 halogen atom(s), cyano, C₁₋₆ alkylthio, halogen atom and heterocyclic carbonyl (e.g., dihydroindolylcarbonyl)]; a C₆₋₁₄ aryl-carboxamide (e.g., benzoylamino); a C₆₋₁₄ arylamino (e.g., phenylamino); a N-C₁₋₁₀ alkyl-N-C₆₋₁₄ arylamino (e.g., N-methyl-N-phenylamino); N-C₁₋₁₀ alkyl-N-C₇₋₁₃ aralkylamino (e.g., N-methyl-N-benzylamino); a mono- or di-C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide); a mono- or di-C₆₋₁₄ aryl-carboxamide (e.g., phenylcarboxamide) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkoxy, C₆₋₁₄ aryloxy and heterocyclic group (e.g., triazolyl, tetrazolyl)]; mono- or di-C₇₋₁₃ aralkyl-carboxamide (e.g., benzylcarboxamide, phenethylcarboxamide, phenylpropylcarboxamide, phenylbutylcarboxamide) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkoxy and halogen atom]; an aromatic heterocyclic-carboxamide (e.g., furylcarboxamide, pyrrolylcarboxamide, thienylcarboxamide, pyridylcarboxamide, pyrimidinylcarboxamide, 1H-indazolylcarboxamide, benzofuranylcarboxamide, quinolylcarboxamide) [optionally substituted by

- 1 to 3 substituent(s) selected from halogen atom and C₁₋₆ alkyl]; a 5- to 7-membered non-aromatic heterocyclic-carboxamide (e.g., tetrahydrofurylcarboxamide, thiomorpholinocarboxamide, piperidinocarboxamide, piperazinocarboxamide, hexamethyleniminylcarboxamide, thiazolidinylcarboxamide) [optionally substituted by 1 to 3 substituent(s) selected from oxo, C₁₋₆ alkoxy-carbonyl, C₁₋₆ alkoxy-C₆₋₁₄ aryl (e.g., methoxyphenyl), C₁₋₆ alkyl-carbonyl-C₆₋₁₄ aryl (e.g., acetylphenyl), carbamoyl, C₇₋₁₃ aralkyl (e.g., benzyl) and heterocyclic group (e.g., piperidino)]; a C₃₋₁₀ cycloalkyl-carboxamide (e.g., cyclopentylcarboxamide, cyclohexylcarboxamide) [optionally substituted by C₁₋₆ alkyl optionally substituted by C₁₋₆ alkoxy-carboxamide (e.g., methoxycarboxamide, ethoxycarboxamide)]; a C₈₋₁₃ arylalkenyl-carboxamide (e.g., styrylcarboxamide) [optionally substituted by halogen atom]; a C₈₋₁₃ arylalkynyl-carboxamide (e.g., phenylethynylcarboxamide); an aromatic heterocyclic (e.g., thienyl, furyl, indolyl)-C₁₋₆ alkyl-carboxamide; a C₆₋₁₄ arylsulfonamino (e.g., phenylsulfonamino); mono- or di-C₁₋₆ alkyl-carbamoylamino (e.g., methylcarbamoylamino, tert-butylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, halogen atom, C₁₋₆ alkoxy-carbonyl, C₁₋₆ alkoxy-carboxamide, cyano, C₁₋₆ alkyl-sulfonyl and carbamoyl]; a C₃₋₁₀ cycloalkyl-carbamoylamino (e.g., cyclopropylcarbamoylamino, cyclopentylcarbamoylamino, cyclohexylcarbamoylamino) [optionally substituted by hydroxy]; a C₆₋₁₄ aryl-carbamoylamino (e.g., phenylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkyl optionally substituted by 1 to 3 halogen atom(s), sulfamoyl optionally substituted by C₁₋₆ alkyl-carbonyl, mono- or di-C₁₋₆ alkylamino, mono- or di-C₁₋₁₀ alkylphosphono-C₁₋₆ alkyl group, halogen atom, C₆₋₁₄ arylsulfonyl (e.g., phenylsulfonyl), a C₇₋₁₃ aralkyloxy (e.g., benzyloxy) and C₁₋₆ alkoxy]; a C₇₋₁₄ aralkyl-carbamoylamino (e.g., benzylcarbamoylamino, phenethylcarbamoylamino, diphenylethylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkyl optionally substituted by 1 to 3 substituent(s) selected from mono- or di-C₁₋₆ alkylamino and halogen atom; halogen atom; sulfamoyl; hydroxyl; and C₁₋₆ alkoxy]; C₁₋₆ alkoxy-carbonylcarbamoylamino (e.g., methoxycarbonylcarbamoylamino, ethoxycarbonylcarbamoylamino); a C₄₋₁₃ cycloalkylalkyl-carbamoylamino (e.g., cyclohexylmethylcarbamoylamino); a heterocyclic (e.g., thienyl, furyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, indolyl, 1H-indazolyl, benzimidazolyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl)-C₁₋₁₀ alkyl-carbamoylamino (e.g., methylcarbamoylamino, ethylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from oxo, C₁₋₆ alkyl, hydroxy and C₁₋₆ alkoxy]; an aromatic heterocyclic carbamoylamino (e.g., isoxazolylcarbamoylamino, benzothiazolylcarbamoylamino) [optionally substituted by 1 to 3 substituent(s) selected from C₁₋₆ alkyl and C₁₋₆ alkoxy]; a non-aromatic heterocyclic carbamoylamino (e.g., pyrrolidinylcarbamoylamino) [optionally substituted by C₁₋₆ alkyl]; or a C₇₋₁₄ aralkyloxy-carbamoylamino (e.g., benzyloxy-carbamoylamino);
- A is (1) —NR²—W—D;
- R² is a hydrogen atom or C₁₋₆ alkyl group, W is a bond or C₁₋₄ alkylene, D is a C₆₋₁₄ aryl group (preferably

- phenyl) optionally substituted by C₁₋₆ alkyl group (preferably methyl, ethyl) optionally substituted by (mono- or di-C₁₋₁₀ alkyl)phosphono group optionally forming a ring (preferably, dimethylphosphono; diethylphosphono; diisopropylphosphono; dibutylphosphono; 2-oxide-1,3,2-dioxaphosphinanyl); or (2) 1-piperidinyl, 1-piperazinyl, 4-morpholinyl or 4-thiomorpholinyl, each optionally having 1 to 3 substituent(s) selected from
- 1) an oxo;
 - 2) a hydroxy;
 - 3) a cyano;
 - 4) a halogen atom (e.g., fluorine, chlorine, bromine, iodine);
 - 5) a C₁₋₆ alkylendioxy (e.g., methylenedioxy, ethylenedioxy)
 - 6) a C₁₋₆ alkyl group (e.g., methyl, ethyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), hydroxyl, cyano, C₁₋₆ alkoxy (e.g., methoxy); an amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl; a 5- or 6-membered aromatic heterocyclic group (e.g., tetrazolyl) optionally substituted by C₁₋₆ alkyl; a 5- or 6-membered non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, thiomorpholino, piperidinyl, pyrrolidinyl, piperazinyl, dioxothiazolidinyl, dioxooxazolidinyl) optionally substituted by C₁₋₆ alkyl; carboxamide; optionally halogenated mono- or di-C₁₋₆ alkyl-carboxamide (e.g., acetylamino, trifluoroacetylamino); and mono- or di-C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide);
 - 7) a C₆₋₁₄ aryl (e.g., phenyl) optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine), optionally halogenated C₁₋₆ alkyl and C₁₋₆ alkoxy;
 - 8) a C₇₋₁₃ aralkyl group (e.g., benzyl, benzhydryl) optionally substituted by C₁₋₆ alkylendioxy;
 - 9) a 5- or 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, piperidinyl, pyrimidinyl, pyrrolidinyl) optionally substituted by a C₁₋₆ alkyl group;
 - 10) an amino (e.g., amino, methylamino, dimethylamino) optionally mono- or di-substituted by C₁₋₆ alkyl;
 - 11) a C₁₋₆ alkyl-carbonyl (e.g., acetyl);
 - 12) a C₁₋₆ alkyl-sulfonyl (e.g., methylsulfonyl, ethylsulfonyl);
 - 13) a C₃₋₁₀ cycloalkyl-carbonyl (e.g., cyclohexylcarbonyl);
 - 14) a C₆₋₁₄ aryl-carbonyl (e.g., benzoyl);
 - 15) a C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl, phenethylcarbonyl);
 - 16) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carbonyl (e.g., styrylcarbonyl);
 - 17) a C₁₋₆ alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl);
 - 18) a 5- or 6-membered aromatic heterocyclic-carbonyl (e.g., furoyl, pyrrolylcarbonyl, thenoyl, pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl;
 - 19) a 5- or 6-membered non-aromatic heterocyclic-carbonyl (e.g., tetrahydrofuroyl) optionally substituted by C₁₋₆ alkyl;
 - 20) a carboxamide;
 - 21) a mono- or di-C₁₋₆ alkyl-carboxamide (e.g., acetylamino, hexanoylamino, trifluoroacetylamino, N-acetyl-N-methylamino, pentafluoropropionylamino)

- optionally substituted by 1 to 3 substituent(s) selected from a halogen atom (e.g., fluorine, chlorine, bromine, iodine) and C₁₋₆ alkyl;
- 22) a C₃₋₁₀ cycloalkyl-carboxamide (e.g., cyclohexylcarboxamide);
 - 23) a C₆₋₁₄ aryl-carboxamide (e.g., phenylcarboxamide) optionally substituted by C₁₋₆ alkylendioxy;
 - 24) a C₇₋₁₃ aralkyl-carboxamide (e.g., benzylcarboxamide, phenethylcarboxamide);
 - 25) a C₆₋₁₄ aryl-C₂₋₆ alkenyl-carboxamide (e.g., styrylcarboxamide);
 - 26) a C₁₋₆ alkoxy-carboxamide (e.g., tert-butoxycarboxamide)
 - 27) a 5- or 6-membered aromatic heterocyclic-carboxamide (e.g., furylcarboxamide, pyrrolylcarboxamide, thienylcarboxamide, pyridylcarboxamide) optionally substituted by C₁₋₆ alkyl;
 - 28) a 5- or 6-membered non-aromatic heterocyclic-carboxamide (e.g., tetrahydrofurylcarboxamide) optionally substituted by C₁₋₆ alkyl;
- [A is preferably the aforementioned (1)];
 B is (1) a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 substituent(s) selected from a C₁₋₆ alkyl (e.g., methyl, ethyl, trifluoromethyl) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a C₁₋₆ alkoxy (e.g., methoxy, ethoxy, trifluoromethoxy) optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine), a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a nitro, a formyl, a C₁₋₃ alkylendioxy (e.g., methylenedioxy), and an aromatic heterocyclic group (e.g., benzofuryl) or (2) a C₁₋₁₀ alkyl group (e.g., methyl, isopropyl, t-butyl);
 [B is preferably a C₆₋₁₄ aryl group (preferably phenyl) optionally substituted by 1 to 3 halogen atom(s) (preferably chlorine, bromine)];
 X is an oxygen atom or a sulfur atom; and
 Y is a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms (preferably C₁₋₄ alkylene).
- Compound (F)
- 3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide;
 - 3-[4-(4-chlorophenyl)-2-(4-morpholinyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide;
 - 3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide;
 - 3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide;
 - 4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[(4-dimethylphosphonomethyl)phenyl]butanamide;
 - 1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol;
 - 4-(3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide;
 - 4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[(4-diethylphosphonomethyl)phenyl]butanamide; or
 - 4-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide.
- As the salts of a compound represented by the formula (I), pharmacologically acceptable salts are preferable. As such salts, for example, a salt with an inorganic base, a salt with

an organic base, a salt with an inorganic acid, a salt with an organic acid and a salt with a basic or acidic amino acid can be mentioned.

Preferable examples of the salt with an inorganic base include alkali metal salts such as sodium salt, potassium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like; and aluminum salt, ammonium salt and the like.

Preferable examples of the salt with an organic base include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, and the like.

Preferable examples of the salt with an inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid and the like.

Preferable examples of the salt with an organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like.

Preferable examples of the salt with a basic amino acid include salts with arginine, lysine and ornithine and the like.

Preferable examples of the salt with an acidic amino acid include salts with aspartic acid, glutamic acid, and the like.

Of these salts, a sodium salt, a potassium salt, hydrochloride and the like are preferred.

A prodrug of the compound (I) means a compound capable of being converted to the compound (I) in vivo by the reaction of an enzyme or gastric juice and the like under physiological conditions, namely a compound capable of being converted to the compound (I) upon enzymatic oxidation, reduction or hydrolysis and the like, or a compound capable of being converted to the compound (I) upon hydrolysis and the like by gastric juice and the like. As the prodrug of the compound (I), compounds derived by acylation, alkylation or phosphorylation of the amino group of the compound (I) (e.g. compounds derived by eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation or tert-butylation of the amino group of the compound (I), and the like); compounds derived by acylation, alkylation, phosphorylation or boration of the hydroxy group of the compound (I) (e.g. compounds derived by acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation or dimethylaminomethylcarbonylation of the hydroxy group of the compound (I), and the like); and compounds derived by esterification or amidation of the carboxyl group of the compound (I) (e.g. compounds derived by ethyl esterification, phenyl esterification; carboxymethyl esterification, dimethylaminomethyl esterification, pivaloyloxymethyl esterification, ethoxycarbonyloxyethyl esterification, phthalidyl esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl esterification, cyclohexyloxycarbonylethyl esterification, or methylamidation of the carboxyl group of the compound (I), and the like), and the like can be mentioned. These compounds can be produced from the compound (I) by methods known per se.

The prodrug of the compound (I) may be one capable of being converted to the compound (I) under physiological conditions, as described in "Iyakuhi no Kaihatsu (Development of Drugs)", vol. 7, Molecular Designing, published by Hirokawa Shoten, 1990, pages 163-198.

The compound (I) may be labeled with an isotope (e.g., ^3H , ^{14}C , ^{35}S , ^{125}I , and the like) and the like.

Furthermore, the compound (I) may be an anhydride or a hydrate.

The compound (I) and a prodrug thereof (hereinafter sometimes to be simply abbreviated as the compound of the present invention) are of lower toxicity and can be used for mammals (e.g. human, mouse, rat, rabbit, dog, cat, cattle, horse, swine, monkey and the like), as an agent for promoting production or secretion of a neurotrophic factor and the like, either as such or by admixing with a pharmacologically acceptable carrier or the like to give a pharmaceutical composition.

Here, as the above-mentioned pharmacologically acceptable carrier, various organic or inorganic carrier substances which are conventionally used as pharmaceutical preparation materials can be mentioned. They are incorporated as excipients, lubricants, binders, disintegrants or the like in solid preparations; as solvents, solubilizers, suspending agents, isotonicizing agents, buffers, soothing agents or the like in liquid preparations. Where necessary, additives such as preservatives, antioxidants, coloring agents, sweeteners and the like may be used.

As preferable examples of the excipients, lactose, sucrose, D-mannitol, D-sorbitol, starch, pre-gelatinized starch, dextrin, crystalline cellulose, low-substituted hydroxypropylcellulose, carboxymethylcellulose sodium, acacia, dextrin, pullulan, light silicic anhydride, synthetic aluminum silicate, magnesium aluminometasilicate and the like can be mentioned.

As preferable examples of the lubricants, magnesium stearate, calcium stearate, talc, colloidal silica and the like can be mentioned.

As preferable examples of the binders, pre-gelatinized starch, sucrose, gelatin, acacia, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, crystalline cellulose, saccharose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the like can be mentioned.

As preferable examples of the disintegrants, lactose, sucrose, starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, carboxymethylstarch sodium, light silicic anhydride, low-substituted hydroxypropylcellulose and the like can be mentioned.

As preferable examples of the solvents, water for injection, physiological saline, Ringer's solution, alcohol, propylene glycol, polyethylene glycol, sesame oil, corn oil, olive oil, cotton seed oil and the like can be mentioned.

As preferable examples of the solubilizers, polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate and the like can be mentioned.

As preferable examples of the suspending agents, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glycerol monostearate and the like; hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like; polysorbates, polyoxyethylene-hardened castor oil, and the like can be mentioned.

As preferable examples of the isotonicizing agents, sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like can be mentioned.

As preferable examples of the buffers, buffer solutions of phosphate, acetate, carbonate, citrate and the like can be mentioned.

As preferable examples of the soothing agents, benzyl alcohol and the like can be mentioned.

As preferable examples of the preservatives, para-oxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like can be mentioned.

As preferable examples of the antioxidants, sulfites, ascorbates and the like can be mentioned.

As preferable examples of the coloring agents, water-soluble edible tar dyes (e.g. food colors such as Food Color Red No. 2 and No. 3, Food Color Yellow No. 4 and No. 5, Food Color Blue No. 1 and No. 2), water-insoluble lake colors (e.g. the aluminum salt of the above water-soluble edible tar dyes and the like), natural colors (e.g. β -carotene, chlorophyll, red iron oxide and the like), and the like can be mentioned.

As preferable examples of the sweeteners, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia and the like can be mentioned.

As the dosage form of the aforementioned pharmaceutical composition, oral preparations such as tablets (including sublingual tablet and intraorally disintegrating tablet), capsules (including soft capsules and microcapsules), granules, powders, troches, syrups, emulsions, suspensions and the like; or parenteral preparations such as injections (e.g. subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection, drip infusions and the like), external preparations (e.g. transdermal preparations, ointments and the like), suppositories (e.g. rectal suppositories, vaginal suppositories and the like), pellets, transnasal agents, transpulmonary agents (inhalant), eye drops etc., and the like can be mentioned, and these preparations can be safely administered orally or parenterally.

These preparations may be controlled-release preparations (e.g., sustained-release microcapsules and the like) such as rapid release preparations, sustained-release preparations and the like.

The pharmaceutical composition can be produced by the methods well established in fields of the pharmaceutical manufacturing techniques, for example, by the methods described in the Japanese Pharmacopoeia and the like. In the following, some concrete methods for producing such preparations are described in detail. The content of the compound of the invention in a pharmaceutical composition varies depending on the dosage form, dose of the compound of the invention and the like, but it is, for example, about 0.1–100 wt %.

For example, an oral preparation can be produced by adding an excipient (e.g., lactose, sucrose, starch, D-mannitol and the like), a disintegrant (e.g., carboxymethylcellulose calcium and the like), a binder (e.g., pre-gelatinized starch, acacia, carboxymethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone and the like), a lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000 and the like) and the like to the active ingredient and compression-molding the mixture, and then, if desirable, by coating the molded product by a method known per se with a coating base for the purpose of masking of taste, or imparting enteric property or durability.

As the coating base, for example, a sugar coating base, a water-soluble film coating base, an enteric film coating base, a sustained-release film coating base and the like can be mentioned.

As the sugar coating base, sucrose is used and, further, one or more kinds of ingredients selected from talc, precipitated calcium carbonate, gelatin, acacia, pullulan, carnauba wax and the like may be used in combination.

As the water-soluble film coating base, for example, cellulose polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose and the like; synthetic polymers such as polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E [Eudragit E (trademark), Roehm Pharma], polyvinylpyrrolidone and the like; polysaccharides such as pullulan and the like, and the like can be mentioned.

As the enteric film coating base, for example, cellulose polymers such as hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylcellulose, cellulose acetate phthalate and the like; acrylic acid polymers such as methacrylic acid copolymer L [Eudragit L (trademark), Roehm Pharma], methacrylic acid copolymer LD [Eudragit L-30D55 (trademark), Roehm Pharma], methacrylic acid copolymer S [Eudragit S (trademark), Roehm Pharma] and the like; natural products such as shellac and the like, and the like can be mentioned.

As the sustained-release film coating base, for example, cellulose polymers such as ethylcellulose and the like; acrylic acid polymers such as aminoalkyl methacrylate copolymer RS [Eudragit RS (trademark), Roehm Pharma], an ethyl acrylate-methyl methacrylate copolymer suspension [Eudragit NE (trademark), Roehm Pharma] and the like; and the like can be mentioned.

Two or more of the above coating bases may be used in admixture in appropriate proportions. On the occasion of coating, a shading agent such as titanium oxide, ferric oxide and the like may be used.

Injections are produced by dissolving, suspending or emulsifying the active ingredient in an aqueous solvent (e.g. distilled water, physiological saline, Ringer's solution) or an oleaginous solvent (e.g. vegetable oils such as olive oil, sesame oil, cotton seed oil, corn oil and the like; propylene glycol and the like), together with dispersants (e.g. polysorbate 80, polyoxyethylene-hardened castor oil 60, polyethylene glycol, carboxymethylcellulose, sodium alginate and the like), preservatives (e.g. methylparaben, propylparaben, benzyl alcohol, chlorobutanol, phenol and the like), isotonicizing agents (e.g. sodium chloride, glycerol, D-mannitol, D-sorbitol, glucose and the like) and the like. If desirable, additives such as solubilizers (e.g. sodium salicylate, sodium acetate and the like), stabilizers (e.g. human serum albumin and the like), soothing agents (e.g. benzyl alcohol and the like) and the like, may be used.

The compound of the present invention has superior neurotrophic factor production or secretion promoting action.

As the neurotrophic factor, for example, neurotrophin, TGF- β superfamily, neurokinin family, growth factor and the like can be mentioned.

The neurotrophin is a general name of the nerve growth factor (NGF) gene family, and refers to a protein that plays an important role in differentiation and functional homeostasis of the cells of the central and peripheral nervous systems, formation of synapse, regeneration and repair of damage and the like. As concrete examples of the neurotrophin, NGF, BDNF (brain-derived neurotrophic factor), NT-3 (neurotrophin-3), NT-4/5 (neurotrophin-4/5), NT-6 (neurotrophin-6) and the like can be mentioned. The neurotrophin preferably includes NGF, BDNF, NT-3 and the like.

The TGF- β superfamily means a protein group known to have a structure characterized by the position of cysteine in a mature molecule, and exhibit a great diversity of actions on various cells and tissues. As concrete examples thereof, TGF- β 1, TGF- β 2, TGF- β 3, BMP (bone morphogenetic protein)-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-

8A, BMP-8B, BMP-14 (GDF-5), GDNF (glial cell line-derived neurotrophic factor), neurturin, artemin, persephin, GDF-1, GDF-8, GDF (growth/differentiation factor)-15, inhibin α , inhibin β , DAF (dauer formation) 7 and the like can be mentioned. The TGF- β superfamily is preferably GDNF, GDF-15 and the like.

As the neurokine family, for example, ciliary neurotrophic factor (CNTF), interleukin 6 (IL-6) and the like can be mentioned.

As the growth factor, for example, insulin growth factor-1 (IGF-1), basic fibroblast growth factor and the like can be mentioned.

The neurotrophic factor is preferably neurotrophin, TGF- β superfamily and the like, more preferably NGF, BDNF, NT-3, GDNF, GDF-15 and the like.

Moreover, the compound of the present invention has a motor nerve or sensory nerve conduction velocity improving action, pain (e.g., neuropathic pain) ameliorating action.

The compound of the present invention is useful as an agent for the prophylaxis or treatment of, for example, neurodegenerative diseases (e.g., Alzheimer's senile dementia, Parkinson's syndrome, Huntington's chorea, amyotrophic lateral sclerosis (ALS), Down's syndrome and the like); peripheral neuropathies (e.g., diabetic neuropathy, cancer treatment-induced neuropathy and the like); diabetic cardiac myopathy; peripheral nerve injury; spinal injury; multiple sclerosis; cerebral ischemic disease; epilepsy; depression; inflammatory bowel disease (e.g., inflammatory colitis and the like); chronic pain (e.g., cancer pain and the like); behavioral abnormalities accompanied by dementia (e.g., wandering, aggressive behavior and the like); anxiety disorder; numbness caused by wound; pain; autonomic abnormalities (e.g., diabetic autonomic disorder, asymptomatic hypoglycemia, gastroparesis, neuropathic diarrhea and constipation, erectile dysfunction, orthostatic hypotension, arrhythmia, heart failure, painless cardiac infarction, dyshidrosis, neuropathic bladder and the like); bladder dysfunction (e.g., bladder reflex disorder and the like); hearing impairment; diabetic foot lesion; bone disease (e.g., osteoporosis and the like); joint disease (e.g., Charcot's joint, osteoarthritis, rheumatism and the like); Hirschsprung's disease; neuropathic pains (e.g., painful neuropathy, postherpetic neuralgia, back pain, trigeminal neuralgia, carpal tunnel syndrome, phantom limb pain, spinal injury, multiple sclerosis); and the like.

In addition, the compound of the present invention is also useful as an agent for the prophylaxis or treatment of diseases such as diabetes (e.g., type-1 diabetes, type-2 diabetes, gestational diabetes etc.), impaired glucose tolerance (IGT), hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, hypo-HDL-emia, postprandial hyperlipidemia and the like), hyperinsulinemia, obesity, hyperphagia, hypertension, cardiovascular disease (e.g., atherosclerosis and the like) and the like; or a syndrome (e.g., syndrome X, visceral obesity syndrome and the like) comprising combination of some of these diseases.

Moreover, the compound of the present invention is used for secondary prophylaxis or suppression of progression (e.g., suppression of progression of impaired glucose tolerance into diabetes) of the above-mentioned various diseases (e.g., cardiac infarction and the like).

Furthermore, the compound of the present invention is useful as an agent for ameliorating peripheral neuropathy or brain metabolic disorder; a promoter of curing skin injury caused by metabolic or endocrine system disease such as diabetes, and by wound; pancreatic regeneration agent (pancreatic function recovering agent); renal regeneration agent

(renal function recovering agent); an agent for ameliorating or suppressing pain (e.g., neuropathic pain); prophylactic agent of amputation of lower limb; a prophylactic agent of sudden death and the like.

While the dose of the compound of the present invention varies depending on the administration subject, administration route, target disease, condition and the like, it is, for example, in the case of oral administration to an adult patient with peripheral neuropathy (e.g., diabetic neuropathy), generally about 0.01–100 mg/kg body weight, preferably 0.05–30 mg/kg body weight, more preferably 0.1–2 mg/kg body weight, per dose, which amount is desirably administered once to 3 times a day.

The compound of the present invention can be used in combination with a pharmaceutical agent (hereinafter to be abbreviated as a combination drug) such as a therapeutic agent of diabetes, a therapeutic agent of diabetic complications, an antihyperlipemic agent, a hypotensive agent, an antiobesity agent, a diuretic, a chemotherapeutic agent, an immunotherapeutic agent, an antithrombotic agent, a therapeutic agent of osteoporosis, an antidementia agent, an agent for ameliorating erectile dysfunction, a therapeutic agent of incontinencia or pollakiuria, an antiepileptic agent, an antidepressant, an opioid agonist, a non-steroidal anti-inflammatory drug, a local anesthetic, vitamins and the like. These combination drugs may be a low molecular weight compound, or may be a high molecular weight protein, polypeptide, antibody, vaccine and the like.

The time of administration of the compound of the present invention and a combination drug is not limited, and these may be administered to an administration subject simultaneously or in a staggered manner. As a concrete mode of administration, for example, (1) administration of a single preparation obtained by simultaneous formulation of the compound of the present invention and a combination drug, (2) simultaneous administration of two kinds of preparations obtained by separate formulation of the compound of the present invention and a combination drug, by the same administration route, (3) time staggered administration of two kinds of preparations obtained by separate formulation of the compound of the present invention and a combination drug, by the same administration route, (4) simultaneous administration of two kinds of preparations obtained by separate formulation of the compound of the present invention and a combination drug, by different administration routes, (5) time staggered administration of two kinds of preparations obtained by separate formulation of the compound of the present invention and a combination drug, by different administration routes, such as administration in the order of the compound of the present invention and then the combination drug, or administration in a reversed order, and the like can be mentioned.

The dose of the combination drug can be appropriately determined based on the dose clinically employed. In addition, the mixing ratio of the compound of the present invention and a combination drug can be appropriately determined according to the administration subject, administration route, target disease, condition, combination and the like. For example, when the administration subject is a human, 0.01–100 parts by weight of a combination drug can be used relative to 1 part by weight of the compound of the present invention.

As the therapeutic agent of diabetes, insulin preparations (e.g. animal insulin preparations obtained by extraction from the bovine or swine pancreas; human insulin preparations synthesized by a genetic engineering technique using *Escherichia coli* or a yeast; insulin-zinc; protamine-insulin-

zinc, a fragment or derivative of insulin (e.g., INS-1 etc.), insulin sensitizers (e.g. pioglitazone hydrochloride, rosiglitazone (maleate), GI-262570, reglinoxane (JTT-501), netoglitazone (MCC-555), YM-440, KRP-297, CS-011, FK-614, the compounds described in WO99/58510 (e.g., (E)-4-[4-
5 (5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid), ragaglitazar (NN-622), AR-H-039242, BMS-298585, EML-16336, tesaglitazar (AZ-242), balaglitazone (NN-2344), ONO-5816, BM-13-1258, LM-4156, MBX-102, LY-519818, MX-6054, LY-510929
10 etc.), α -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate etc.), biguanides (e.g., phenformin, metformin, buformin etc.), insulin secretagogues [sulfonyleureas (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glycopyramide, glimepiride, glipizide, glybuzole etc.), repaglinide, senaglinide, nateglinide, mitiglinide or its calcium salt hydrate etc.], GLP-1 receptor agonists [e.g., GLP-1, NN-2211, AC-2993 (exendin-4), BIM-51077, Aib(8,35)hGLP-1(7,37)NH₂,
15 etc.], amylin agonists (e.g., pramlintide etc.), phosphotyrosine phosphatase inhibitors (e.g., vanadic acid etc.), dipeptidylpeptidase IV inhibitors (e.g., NVP-DPP-278, PT-100, P32/98 etc.), β 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 etc.), gluconeogenesis inhibitors (e.g., glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists etc.), SGLT (sodium-glucose cotransporter) inhibitors (e.g., T-1095 etc.) and the like can be mentioned.

As the therapeutic agent of diabetic complications, aldose reductase inhibitors (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat, SNK-860, CT-112 and the like), neurotrophic factors and increasing drugs thereof (e.g., NGF, NT-3, BDNF, neurotrophin production or secretion promoters described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole and the like) and the like), nerve
20 regeneration enhancers (e.g., Y-128 and the like), PKC inhibitors (e.g., LY-333531 and the like), AGE inhibitors (e.g., ALT946, pimagedine, pyratoxanthine, N-phenacylthiazolium bromide (ALT766), EXO-226 and the like), active
25 oxygen scavengers (e.g., thioctic acid and the like), cerebral vasodilators (e.g., tiapride, mexiletine and the like), and the like can be mentioned.

As the antihyperlipemic agent, statin compounds (e.g., cerivastatin, pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, itavastatin and salts thereof (e.g., sodium salt) and the like) which are cholesterol synthesis inhibitors, squalene synthase inhibitors (e.g., compounds described in WO97/10224, such as N-[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,
30 3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]-piperidine-4-acetic acid and the like), fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, clinofibrate and the like) having a triglyceride lowering action, and the like can be mentioned.

As the hypotensive agent, angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril and the like) r angiotensin II antagonists (e.g., candesartan cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan, asosartan etc.), calcium antagonists (e.g., manidipine, nifedipine,
35 amlodipine, efonidipine, nicardipine and the like), clonidine and the like can be mentioned.

As the antiobesity agent, for example, antiobesity drugs acting on the central nervous system (e.g. dexfenfluramine, fenfluramine, phentermine, sibutramine, anfepramon, dex-
40 amphetamine, mazindol, phenylpropanolamine, clobenzorex, and the like), pancreatic lipase inhibitors (e.g., orlistat

etc.), β 3 agonists (e.g., CL-316243, SR-58611-A, UL-TG-307, SB-226552, AJ-9677, BMS-196085, AZ40140 etc.), anorectic peptides (e.g., leptin, CNTF (ciliary neurotrophic factor) etc.), cholecystokinin agonists (e.g., lintitript, FPL-
5 15849 etc.) and the like can be mentioned.

As the diuretic, for example, xanthine derivatives (e.g., sodium salicylate and theobromine, calcium salicylate and theobromine, and the like), thiazide preparations (e.g., ethiazide, cyclopenthiiazide., trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzyhydrochlorothiazide,
10 penflutizide, polythiazide, methyclothiazide and the like), antialdosterone preparations (e.g., spironolactone, triamterene and the like), carbonic anhydrase inhibitors (e.g., acetazolamide and the like), chlorobenzenesulfonamide
15 preparations (e.g., chlortalidone, mefruside, indapamide and the like), azosemide, isosorbide, etacrynic acid, piretanide, bumetanide, furosemide and the like can be mentioned.

As the chemotherapeutic agent, for example, alkylation agents (e.g., cyclophosphamide, ifosfamide and the like),
20 metabolic antagonists (e.g., methotrexate, 5-fluorouracil and the like), anti-cancer antibiotics (e.g., mitomycin, adriamycin and the like), plant-derived anti-cancer agents (e.g., vincristin, vindesine, taxol and the like), cisplatin, carboplatin, etoposide and the like can be mentioned. Of these,
25 furtulon and neofurtulon, which are 5-fluorouracil derivatives, and the like are preferable.

As the immunotherapeutic agent, for example, microorganism or bacterial components (e.g., a muramyl dipeptide derivative, picibanil and the like), polysaccharides having
30 immunity potentiating activity (e.g., lentinan, sizofiran, krestin and the like), cytokines obtained by genetic engineering techniques (e.g., interferon, interleukin (IL) and the like), colony stimulating factors (e.g., granulocyte colony stimulating factor, erythropoietin and the like) and the like
35 can be mentioned, with preference given to IL-1, IL-2, IL-12 and the like.

As the antithrombotic agent, for example, heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium and the like), warfarin (e.g., warfarin potassium and the like), anti-
40 thrombin drugs (e.g., aragatroban and the like), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, mon-teplase, pamiteplase and the like), platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride
45 and the like) and the like can be mentioned.

As the therapeutic agent of osteoporosis, for example, alfacalcidol, calcitriol, elcatonin, calcitonin salmon, estriol, ipriflavone, pamidronate disodium, alendronate sodium
50 hydrate, incadronate disodium and the like can be mentioned.

As the antidementia agent, for example, tacrine, donepezil, rivastigmine, galantamine and the like can be mentioned.

As the agent for ameliorating erectile dysfunction, for example, apomorphine, sildenafil citrate and the like can be mentioned.

As the therapeutic agent of incontinencia or pollakiuria, for example, flavoxate hydrochloride, oxybutynin hydrochloride, propiverine hydrochloride and the like can be mentioned.

As the antiepileptic agent, for example, gabapentin, carbamazepine and the like can be mentioned.

As the antidepressant, for example, amitriptyline, imipramine and the like can be mentioned.

As the opioid agonist, for example, morphine and the like can be mentioned.

As the non-steroidal anti-inflammatory drug, for example, aspirin, acetaminophen, indomethacin and the like can be mentioned.

As the local anesthetic, for example, lidocaine, capsaicin and the like can be mentioned.

As vitamins, for example, vitamin B1, vitamin B12 and the like can be mentioned.

Furthermore, drugs having a cachexia-ameliorating action established in animal models or clinical situations, such as cyclooxygenase inhibitors (e.g., indomethacin and the like) [*Cancer Research*, Vol. 49, 5935–5939, 1989], progesterone derivatives (e.g., megestrol acetate) [*Journal of Clinical Oncology*, Vol. 12, 213–225, 1994], glucocorticoid (e.g., dexamethasone and the like), metoclopramide agents, tetrahydrocannabinol agents (ibid.), fat metabolism improving agents (e.g., eicosapentaenoic acid and the like) [*British Journal of Cancer*, Vol. 68, 314–318, 1993], growth hormones, IGF-1, or antibodies to a cachexia-inducing factor such as TNF- α , LIF, IL-6, Oncostatin M and the like, can be also used in combination with the compound of the present invention.

The combination drug is preferably an insulin preparation, an insulin sensitizer, α -glucosidase inhibitor, a biguanide, an insulin secretagogue (preferably a sulfonylurea), an aldose reductase inhibitor, a PKC inhibitor, an antiepileptic agent, an antidepressant, an opioid agonist, a non-steroidal anti-inflammatory drug and the like.

The above-mentioned combination drugs may be used in combination of two or more kinds at an appropriate ratio. As preferable combinations when two or more kinds of the combination drugs are used, for example, the following can be mentioned.

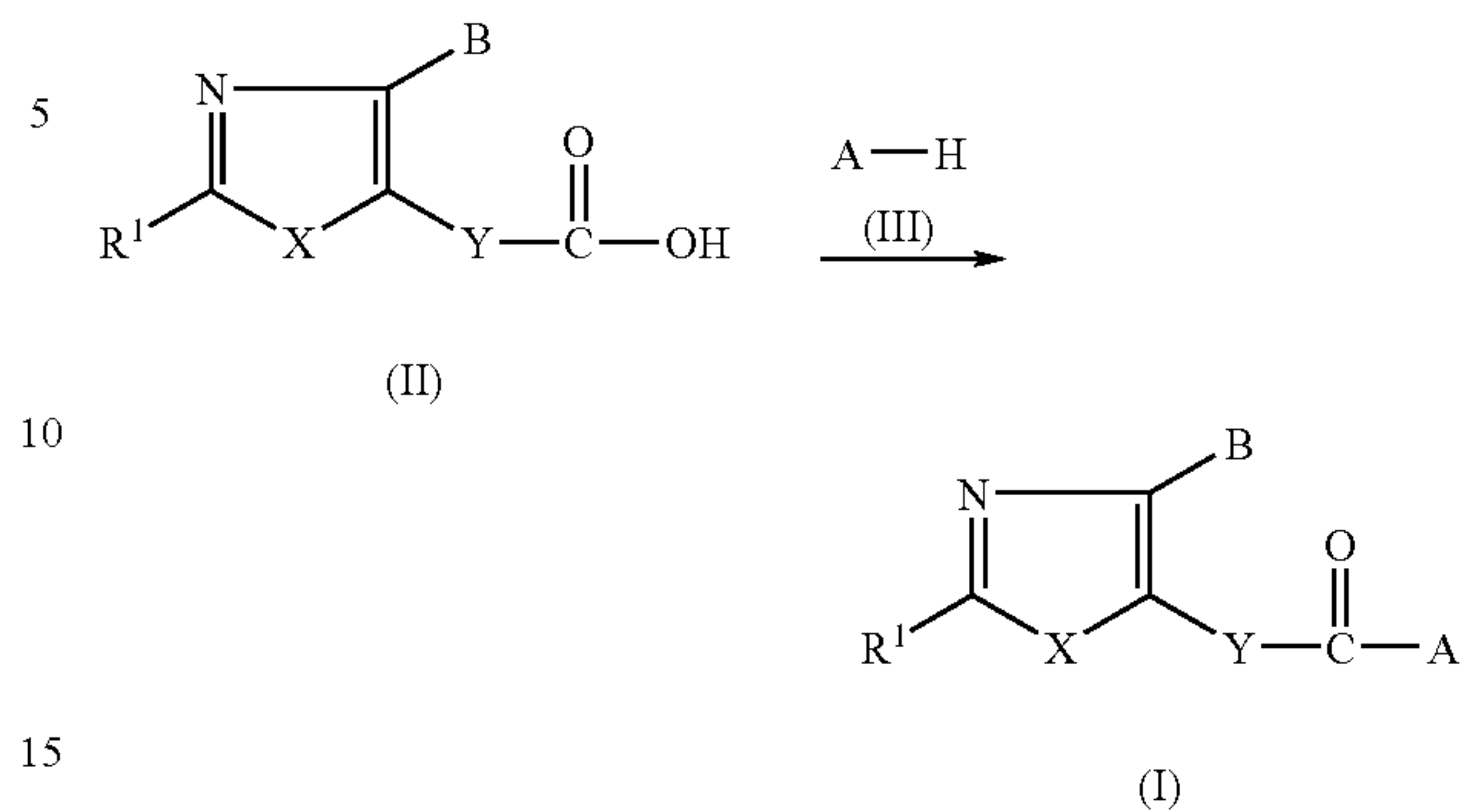
- 1) an insulin secretagogue (preferably a sulfonylurea) and an α -glucosidase inhibitor;
- 2) an insulin secretagogue (preferably a sulfonylurea) and a biguanide;
- 3) an insulin secretagogue (preferably a sulfonylurea), a biguanide and an α -glucosidase inhibitor;
- 4) an insulin sensitizer and an α -glucosidase inhibitor;
- 5) an insulin sensitizer and a biguanide;
- 6) an insulin sensitizer, a biguanide and an α -glucosidase inhibitor.

When the compound of the present invention is used in combination with a combination drug, the dose of the both components can be reduced within a safe range in consideration of the opposing effect of the components. Particularly, a combination drug such as an insulin sensitizer, an insulin secretagogue (preferably a sulfonylurea) and a biguanide can be reduced from the normal dose. Therefore, the opposing effect caused by these agents can be safely prevented. In addition, the doses of a therapeutic agent of diabetic complications, an antihyperlipemic agent and a hypotensive agent can be reduced, and as a result, the side effects that would be caused by these agents can be prevented effectively.

The production methods of the compound of the present invention are explained in the following.

The compound (I) can be produced by, for example, the following Methods A–G, or a method analogous thereto.

[Method A]



wherein the symbols are as defined above.

In this method, compound (II) is subjected to an amidation reaction to produce compound (I). This reaction is carried out according to a method known per se, such as a method for directly condensing compound (II) with compound (III) using a condensation agent, a method for appropriately reacting a reactive derivative of compound (II) with compound (III) and the like.

As the condensation agent, one such as carbodiimide type condensation reagents such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-dimethylaminopropylcarbodiimide or its hydrochloride and the like; phosphoric acid type condensation reagents such as diethyl cyanophosphate, diphenylphosphoryl azide and the like; carbonyl diimidazole, 2-chloro-1,3-dimethylimidazolium tetrafluoroborate and the like can be mentioned.

As a solvent to be used for the reaction using a condensation agent, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate, water and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at appropriate ratios.

The amount of compound (III) to be used is generally 0.1–10 molar equivalents, preferably 0.3–3 molar equivalents, relative to compound (II).

The amount of the condensation agent to be used is generally 0.1–10 molar equivalents, preferably 0.3–3 molar equivalents, relative to compound (II).

When the aforementioned carbodiimide type condensation reagent is used as the condensation agent, the reaction efficiency can be improved by the use of a suitable condensation promoter (e.g., 1-hydroxy-7-azabenzotriazole, 1-hydroxybenzotriazole, N-hydroxysuccinimide, N-hydroxyphthalimide and the like) where necessary. When the above-mentioned phosphoric acid type condensation reagent is used as the condensation agent, the reaction efficiency can be improved by generally adding an organic amine type base such as triethylamine and the like.

The amount of the above-mentioned condensation promoter and the organic amine type base to be used is generally 0.1–10 molar equivalents, preferably 0.3–3 molar equivalents, relative to compound (II).

The reaction temperature is generally -30°C . to 100°C .

The reaction time is generally 0.5–60 hrs.

In the method using a reactive derivative of compound (II), as the reactive derivative of compound (II), for

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example, acid anhydride, acid halide (acid chloride, acid bromide), imidazolide, or mixed acid anhydride (e.g., anhydride with methyl carbonate, ethyl carbonate or isobutyl carbonate, and the like) and the like can be mentioned.

For example, when an acid anhydride or an acid halide is used as the reactive derivative, the reaction is generally carried out in the presence of a base, in a solvent that does not exert an influence on the reaction.

As the base, for example, amines such as triethylamine, pyridine, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like can be mentioned.

The amount of the base to be used is generally 0.1–10 molar equivalents, preferably 0.3–3 molar equivalents, relative to compound (II).

As the solvent that does not exert an influence on the reaction, for example, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; aromatic hydrocarbons such as benzene, toluene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ethyl acetate, water and the like can be mentioned. Two or more kinds of these solvents may be used in a mixture at appropriate ratios. When the above-mentioned amides are used as the solvent that does not exert an influence on the reaction, the reaction can be also carried out in the absence of a base.

The amount of compound (III) to be used is generally 0.1–10 molar equivalents, preferably 0.3–3 molar equivalents, relative to compound (II).

The reaction temperature is generally -30°C . to 100°C .
The reaction time is generally 0.5–20 hrs.

When a mixed acid anhydride is used, compound (II) is reacted with chlorocarbonic acid esters (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, isobutyl chlorocarbonate and the like) in the presence of a base and then reacted with compound (III).

As the base, for example, amines such as triethylamine, aniline, N-methylmorpholine, N,N-dimethylaniline, 4-dimethylaminopyridine and the like; alkali metal salts such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like can be mentioned.

The amount of the base to be used is generally 0.1–10 molar equivalents, preferably 0.3–3 molar equivalents, relative to compound (II).

The amount of the compound (III) to be used is generally 0.1–10 molar equivalents, preferably 0.3–3 molar equivalents, relative to compound (II).

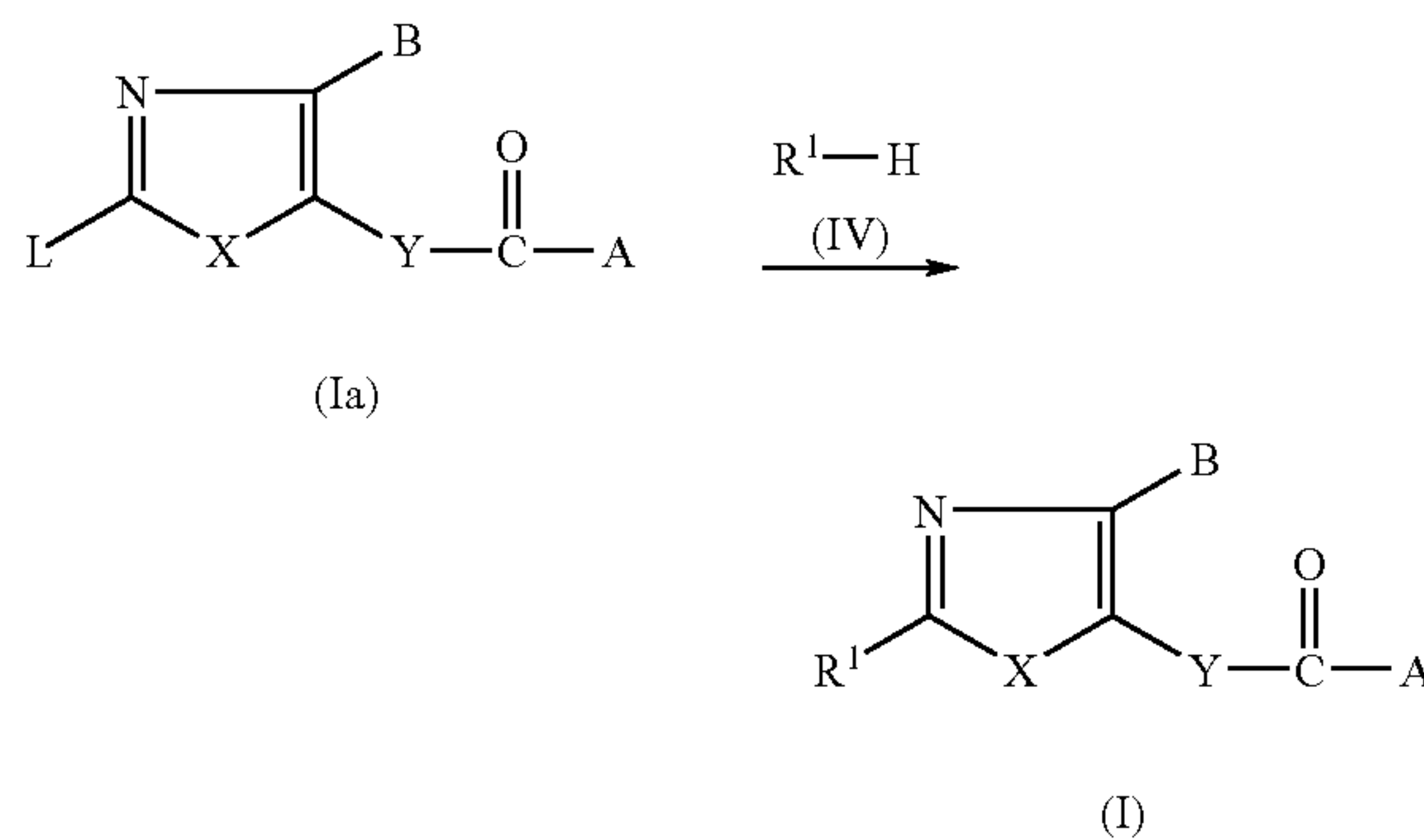
The reaction temperature is generally -30°C . to 100°C .
The reaction time is generally 0.5–20 hrs.

The compound (I) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, a method using an ion exchange resin and a scavenger resin and the like.

The compound (II) to be used as a starting compound in the above-mentioned Method A can be produced by a method described in, for example, WO97/36882, WO01/14372 and the like, or a method analogous thereto. In addition, compound (III) can be produced by a method known per se.

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[Method B] (Substitution Reaction)



wherein L is a leaving group, and other symbols are as defined above.

As the leaving group for L, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine); an oxygen functional group such as alkoxy group, phenoxy group and the like; a sulfur functional group such as sulfanyl group, sulfinyl group, sulfonyl group and the like; an amino group; an acyl group and the like can be mentioned.

In this method, compound (Ia) is reacted with compound (IV) to give compound (I).

This reaction is carried out according to a conventional method generally in the presence of a base in a solvent that does not exert an adverse influence on the reaction.

As the base, for example, alkali metal salts such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like; alkaline earth metal salts such as barium carbonate, calcium carbonate, barium hydroxide, calcium hydroxide and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and the like; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; and the like can be mentioned.

The amount of the base to be used is preferably about 1–about 5 molar equivalents., relative to compound (Ia).

As the solvent that does not exert an adverse influence on the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like, water and the like can be mentioned. These solvents may be used in a mixture at appropriate ratios.

The reaction temperature is generally about -50°C . to about 150°C ., preferably about -10°C . to about 100°C .

The reaction time is generally about 0.5–about 20 hrs.

The compound (I) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, a method using an ion exchange resin and a scavenger resin and the like.

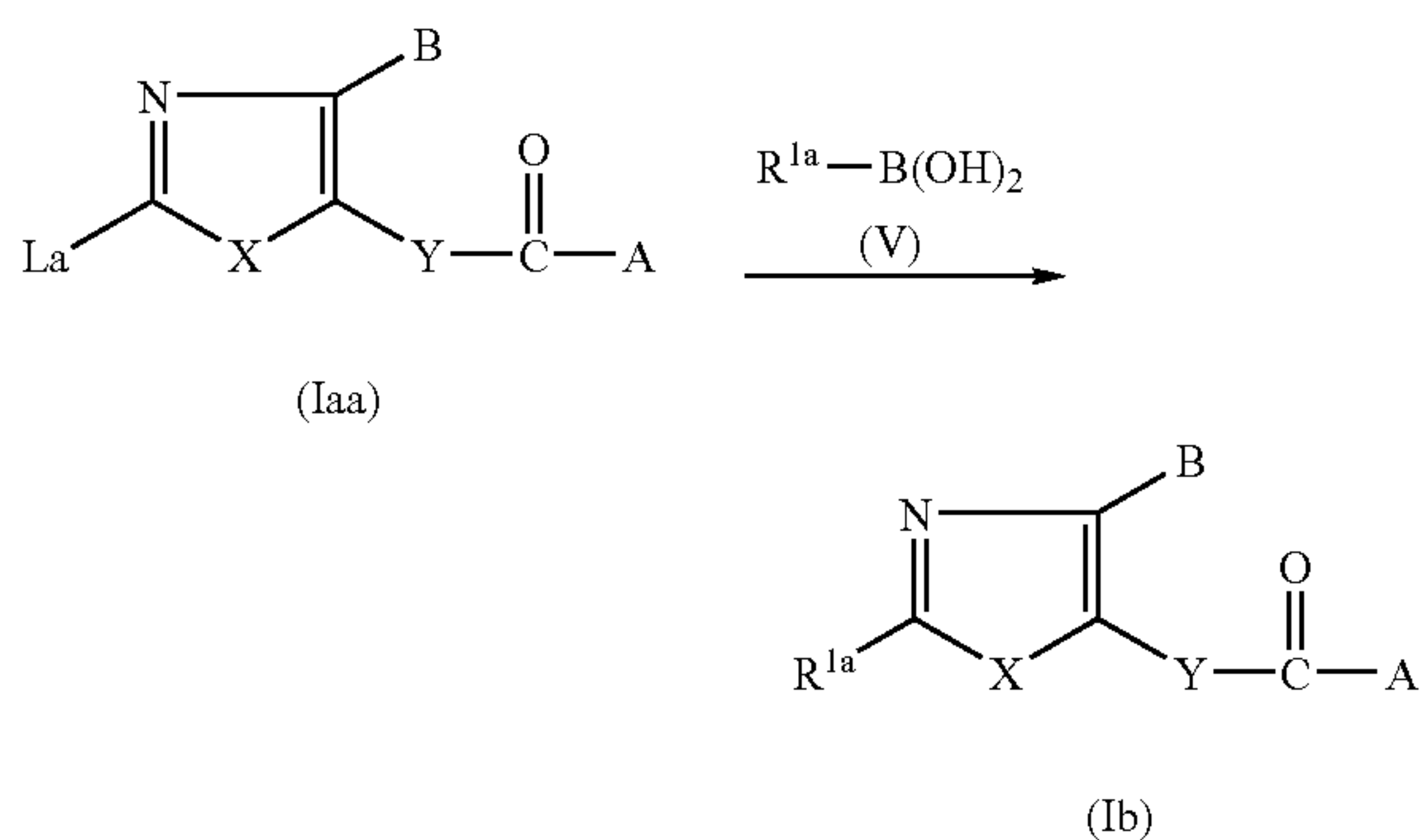
The compound (Ia) to be used as a starting compound in the above-mentioned Method B can be produced according

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to the aforementioned Method A. In addition, compound (IV) can be produced by a method known per se.

The compound (Ib) having an optionally substituted aryl group for R^{1a} in the formula (I) can be also produced by the following Method C.

[Method C] (Suzuki Coupling Reaction)



wherein La is a halogen atom, R^{1a} is an optionally substituted aryl, and other symbols are as defined above.

As the halogen atom for La , fluorine, chlorine, bromine and iodine can be mentioned.

As the “optionally substituted aryl group” for R^{1a} , one from those exemplified for the “optionally substituted hydrocarbon group” for R^1 , wherein the “hydrocarbon group” is an aryl group, can be mentioned. Particularly, phenyl optionally substituted by 1 or 2 substituent(s) selected from C_{1-6} alkyl and halogen atom, and the like are preferable.

Specific examples of compound (V) include phenylboronic acid, tolylboronic acid, 4-fluorophenylboronic acid and the like.

This method is performed according to known Suzuki reaction (*Journal of Organometallic Chemistry*, vol. 576, p. 147 (1999)).

That is, in this method, compound (Iaa) and compound (V) are reacted in the presence of a suitable base as necessary and using a palladium catalyst to give compound (Ib).

This reaction is performed according to a conventional method generally in the presence of a base in a solvent that does not exert an adverse influence on the reaction.

As the base, for example, alkali metal salts such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like; alkaline earth metal salts such as barium carbonate, calcium carbonate, barium hydroxide, calcium hydroxide and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium t.-butoxide and the like; and the like can be mentioned.

The amount of the base to be used is preferably about 1–about 5 molar equivalents, relative to compound (Iaa).

The amount of compound (V) to be used is preferably about 1–about 5 molar equivalents, relative to compound (Iaa).

As the solvent that does not exert an adverse influence on the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tet-

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rahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like, water and the like can be mentioned. These solvents may be used in a mixture at appropriate ratios.

The reaction temperature is generally about -50°C . to about 150°C ., preferably about -10°C . to about 100°C .

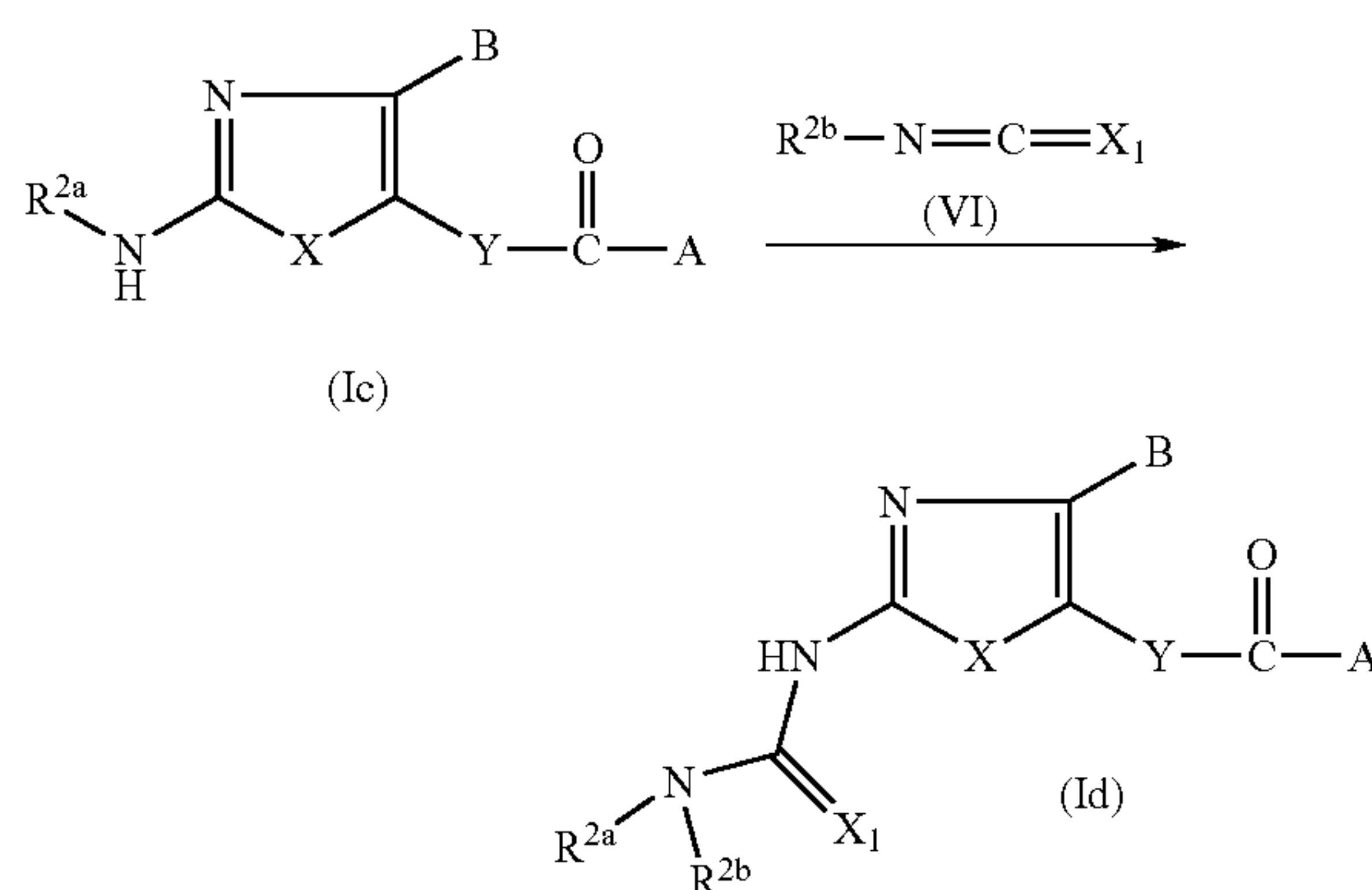
The reaction time is generally about 0.5–about 20 hrs.

The compound (Ib) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, a method using an ion exchange resin and a scavenger resin and the like.

The compound (Iaa) to be used as a starting compound in the above-mentioned Method C can be produced by, for example, the aforementioned Method A. In addition, compound (V) can be produced by a method known per se.

The compound (Id) wherein, in the formula (I), R^1 is an amino group optionally substituted by carbamoyl or thio-carbamoyl can be also produced by the following Method D.

[Method D] (Reaction Between Aminoazole and Isocyanate Derivative)



wherein X_1 is an oxygen atom or a sulfur atom, R^{2a} is a hydrogen atom or an optionally substituted alkyl group, R^{2b} is an optionally substituted alkyl group or an optionally substituted aryl group, and other symbols are as defined above.

As the “optionally substituted alkyl group” for R^{2a} or R^{2b} , one from those exemplified for the “optionally substituted hydrocarbon group” for R^1 , wherein the “hydrocarbon group” is an alkyl group, can be mentioned. Particularly, C_{1-6} alkyl and the like are preferable.

As the “optionally substituted aryl group” for R^{2b} , one from those exemplified for the “optionally substituted hydrocarbon group” for R^1 , wherein the “hydrocarbon group” is an aryl group, can be mentioned. Particularly, phenyl and the like are preferable.

Specific examples of compound (VI) include, phenyl isocyanate, isopropyl isocyanate, phenylthio isocyanate and the like.

In this method, compound (Ic) and compound (IV) are reacted to give compound (Id).

This reaction is performed according to a conventional method generally under neutral conditions and where nec-

essary, in the presence of a suitable base in a solvent that does not exert an adverse influence on the reaction.

As the base, for example, alkali metal salts such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like; alkaline earth metal salts such as barium carbonate, calcium carbonate, barium hydroxide, calcium hydroxide and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like and the like can be mentioned.

The amount of the base to be used is preferably about 1–about 5 molar equivalents, relative to compound (Ic).

The amount of compound (VI) to be used is preferably about 1–about 5 molar equivalents, relative to compound (Ic).

As the solvent that does not exert an adverse influence on the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like; amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like and the like can be mentioned. These solvents may be used in a mixture at appropriate ratios.

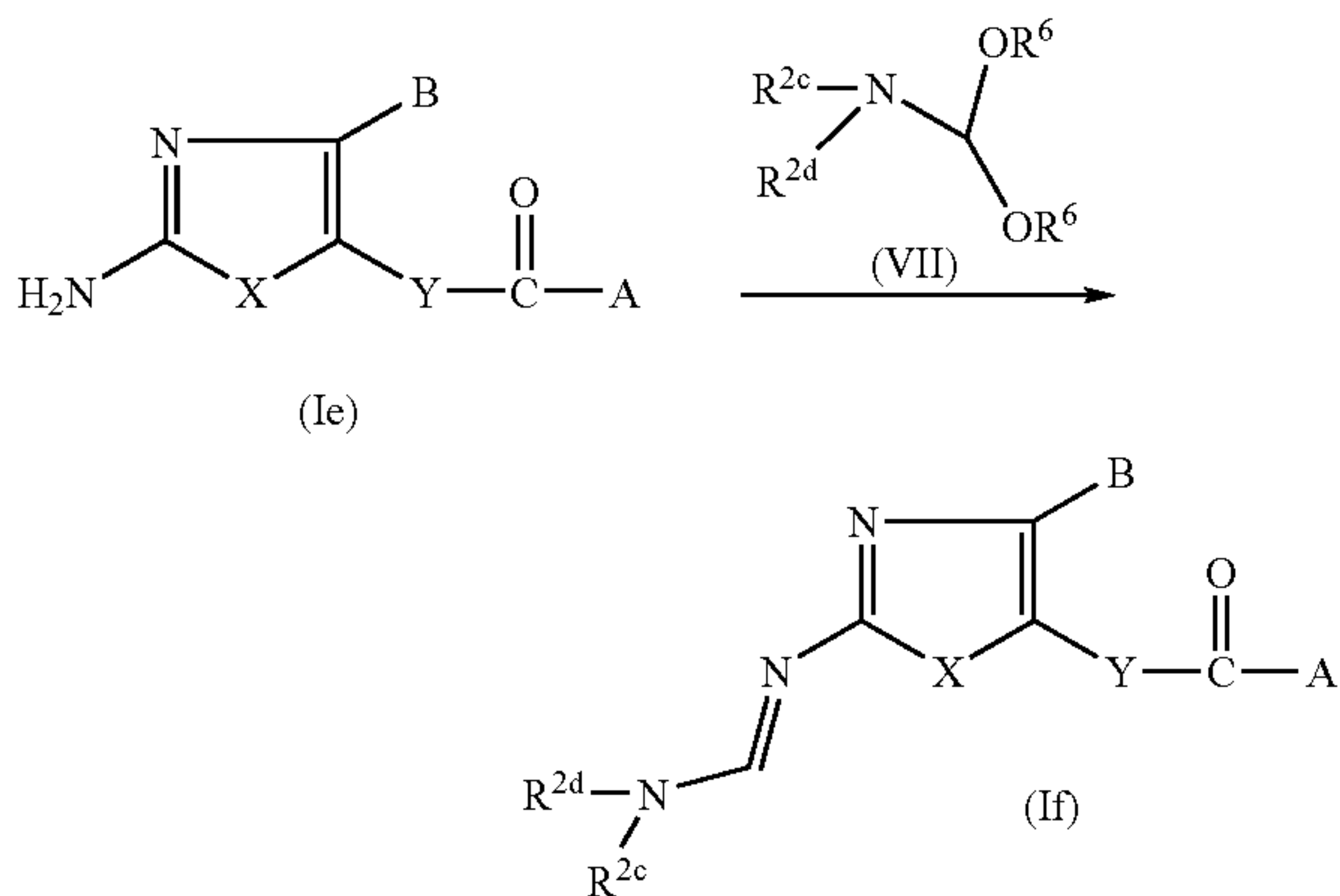
The reaction temperature is generally about -50°C . to about 150°C ., preferably about -10°C . to about 100°C .

The reaction time is generally about 0.5–about 20 hrs.

The compound (Id) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, a method using an ion exchange resin and a scavenger resin and the like.

The compound (Ic) to be used as a starting compound in the above-mentioned Method D can be produced by, for example, the aforementioned Method A or Method B. In addition, compound (VI) can be produced by a method known per se.

[Method E] (Reaction Between Aminoazole and Acetal Derivative)



wherein R^{2c} and R^{2d} are the same or different and each is a hydrogen atom, an optionally substituted alkyl group or an

optionally substituted aryl group, R^6 is a C_{1-6} alkyl group, and other symbols are as defined above.

As the “optionally substituted alkyl group” and “optionally substituted aryl group” for R^{2c} and R^{2d} , those exemplified for the aforementioned R^{2b} can be mentioned.

As the C_{1-6} alkyl group for R^6 , those exemplified for the aforementioned R^2 can be mentioned.

In this method, compound (Ie) and compound (VII) are reacted to give compound (If).

This reaction is performed according to a conventional method generally under neutral conditions and where necessary, in the presence of a suitable base, in a solvent that does not exert an adverse influence on the reaction.

As the base, for example, alkali metal salts such as lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium carbonate, cesium carbonate and the like; alkaline earth metal salts such as barium carbonate, calcium carbonate, barium hydroxide, calcium hydroxide and the like; amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene and; metal hydrides such as potassium hydride, sodium hydride and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; and the like can be mentioned.

The amount of the base to be used is preferably about 1–about 5 molar equivalents, relative to compound (Ie).

The amount of compound (VII) to be used is preferably about 1–about 5 molar equivalents, relative to compound (Ie).

As the solvent that does not exert an adverse influence on the reaction, for example, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as tetrahydrofuran, dioxane, diethyl ether and the like; ketones such as acetone, 2-butanone and the like; halogenated hydrocarbons such as chloroform, dichloromethane and the like;

amides such as N,N-dimethylformamide and the like; sulfoxides such as dimethyl sulfoxide and the like, water and the like can be mentioned. These solvents may be used in a mixture at appropriate ratios.

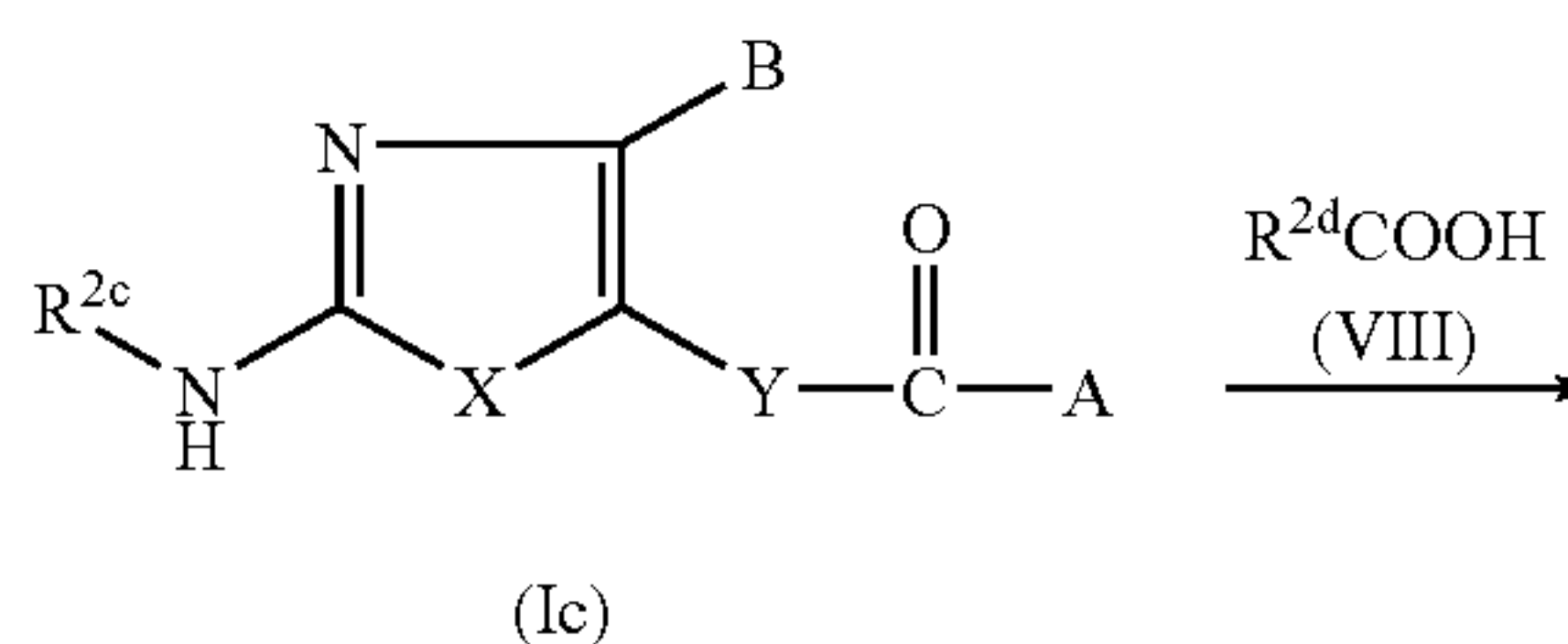
The reaction temperature is generally about -50°C . to about 150°C ., preferably about -10°C . to about 100°C .

The reaction time is generally about 0.5–about 20 hrs.

The compound (If) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, a method using an ion exchange resin and a scavenger resin and the like.

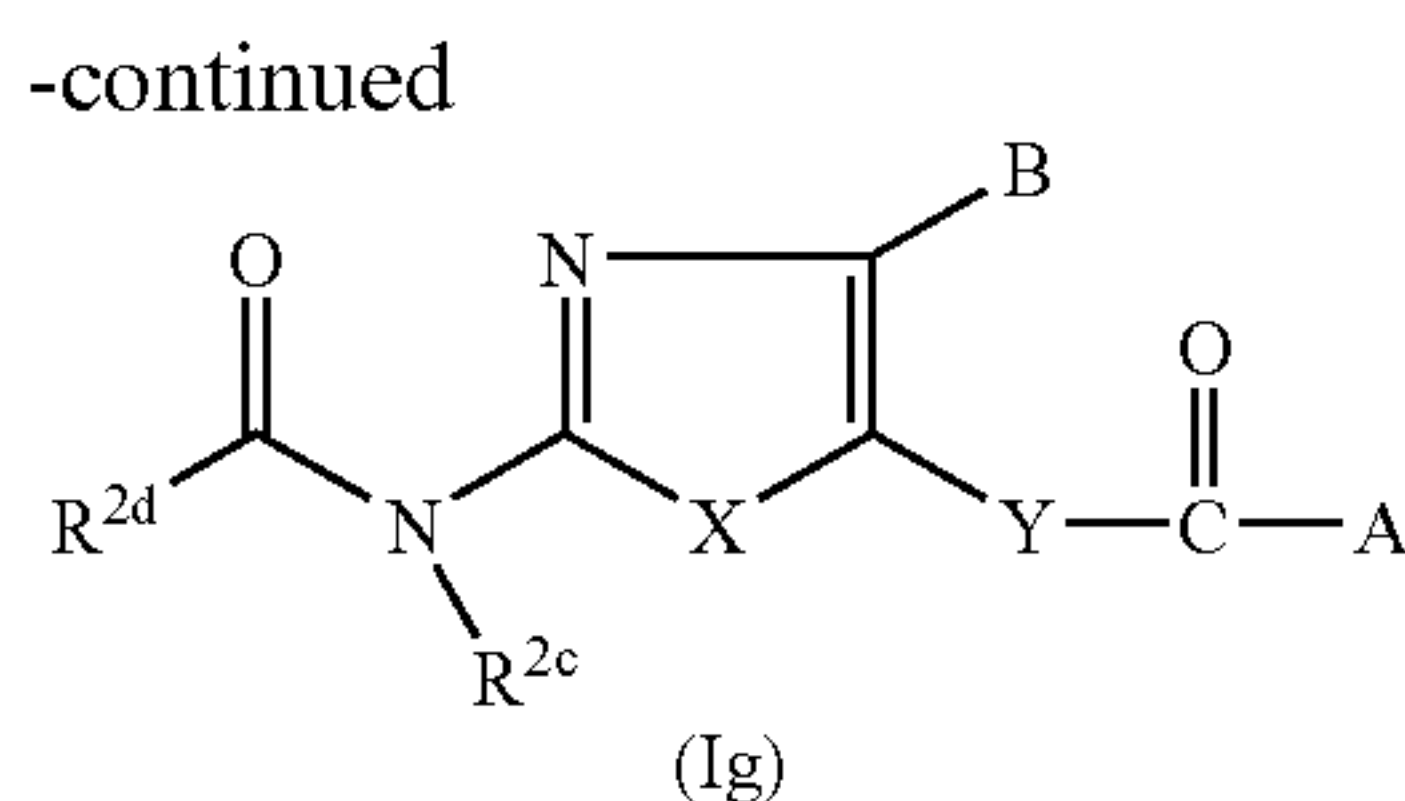
The compound (Ie) to be used as a starting compound in the above-mentioned Method E can be produced by, for example, the aforementioned Method A or Method B. In addition, compound (VII) can be produced by a method known per se.

[Method F] (Reaction Between Aminoazole and Carboxylic Acid Derivative)



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wherein the symbols are as defined above.

In this method, compound (Ic) and compound (VIII) are reacted to give compound (Ig).

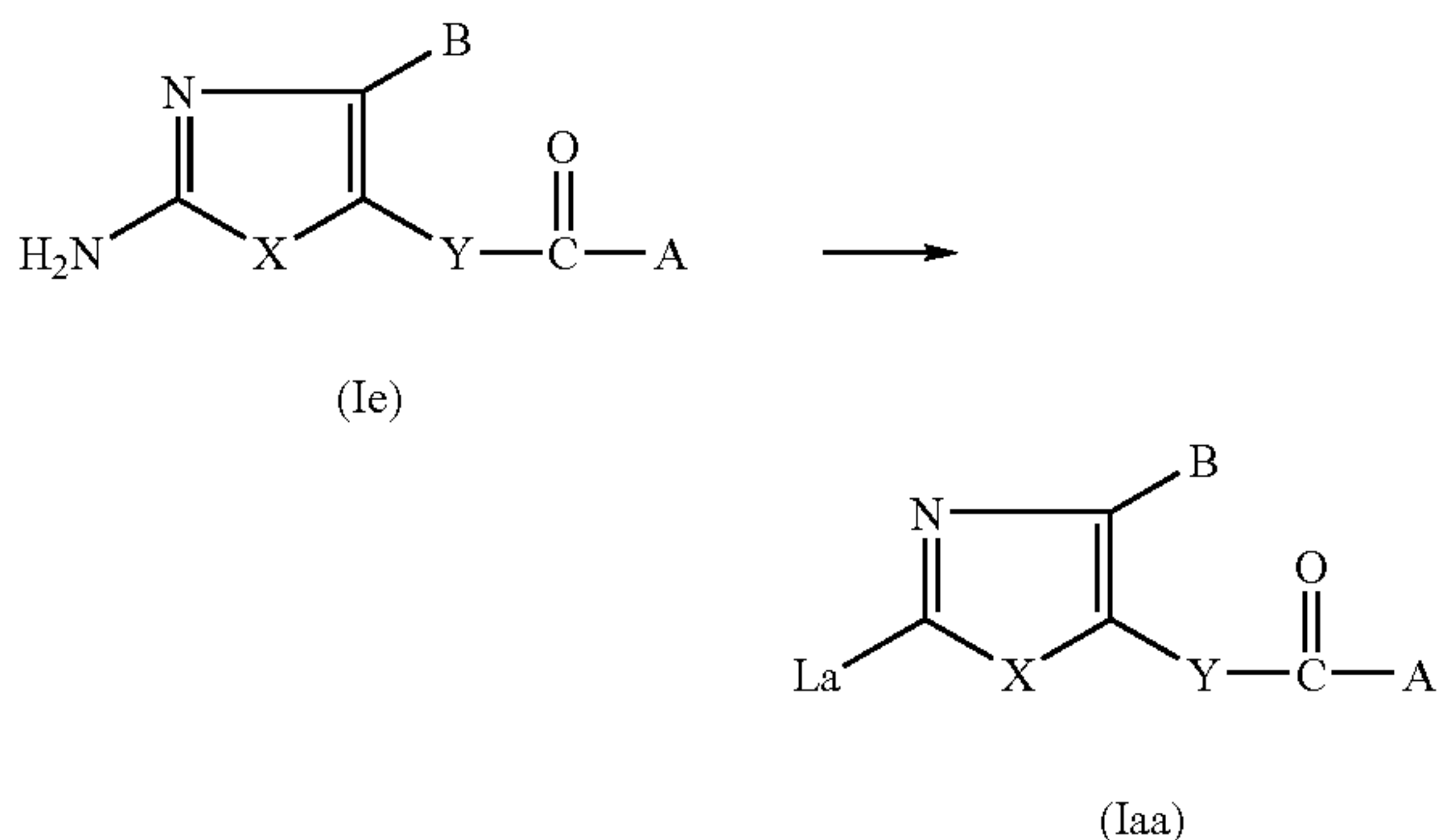
This method can be performed in the same manner as in the aforementioned Method A.

The compound (Ig) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, a method using an ion exchange resin and a scavenger resin and the like.

The compound (Ic) to be used as a starting compound in the above-mentioned Method F can be produced by, for example, the aforementioned Method A or Method B. In addition, compound (VIII) can be produced by a method known per se.

Of the compound (Ia) used as a starting compound in the aforementioned Method B, compound (Iaa) wherein the leaving group for L is a halogen atom, and compound (Iaa) to be used as a starting compound in Method C can be produced by, for example, the following Method G.

[Method G] Sandmeyer Reaction of Aminoazole



wherein the symbols are as defined above.

This reaction is performed according to, for example, a known Sandmeyer reaction.

That is, compound (Ie) is subjected to diazotization reaction, the obtained diazonium salt and a monovalent or divalent copper salt and hydrochloric acid or hydrobromic acid are reacted in a solvent that does not exert an adverse influence on the reaction to give compound (Iaa).

The diazotization reaction is carried out using a diazotization reagent according to a known method. As the diazotization reagent, for example, nitrous acid, nitrites such as sodium nitrite and the like; nitrosyl halides such as nitrosyl chloride and the like; and the like are used.

The amount of the diazotization reagent to be used is generally about 1–about 5 molar equivalents, relative to compound (Ie).

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As the monovalent or divalent copper salt, copper(I) chloride, copper(I) bromide, copper(I) iodide, copper(II) chloride, copper(II) bromide, copper(II) iodide and the like can be mentioned.

The amount of the copper salt to be used is generally about 1–5 molar equivalents, relative to compound (Ie).

As the solvent that does not exert an adverse influence on the reaction, for example, alcohols such as methanol, ethanol and the like; ethers such as tetrahydrofuran, dioxane and the like; aromatic amines such as quinoline, pyridine and the like; acetone, dimethyl sulfoxide, phosphoric acid, acetic acid, water and the like can be mentioned. These solvents may be used in a mixture at appropriate ratios.

The reaction temperature is generally about -20° C. to 200° C., preferably about 0° C. to 150° C.

The reaction time is generally about 0.5–about 20 hrs.

This reaction can be also carried out by reacting compound (Ie) with alkyl nitrite in the presence of a monovalent or divalent copper salt in a solvent that does not exert an influence on the reaction.

As the monovalent or divalent copper salt, those similar to the aforementioned examples can be mentioned. The amount of copper salt to be used is generally about 1–5 molar equivalents, relative to compound (Ie).

As the solvent that does not exert an influence on the reaction, for example, ethers such as tetrahydrofuran, dioxane and the like; acetonitrile, acetone, dimethyl sulfoxide and the like can be mentioned. These solvents may be used in a mixture at appropriate ratios.

As the alkyl nitrite, for example, t-butyl nitrite, isoamyl nitrite and the like can be mentioned. The amount of alkyl nitrite to be used is generally about 1–5 molar equivalents, relative to compound (Ie).

The reaction temperature is generally about -20° C. to 200° C., preferably about 0° C. to 150° C.

The reaction time is generally about 0.5–about 20 hrs.

The compound (Iaa) thus obtained can be isolated and purified by a known separation and purification means, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography, a method using an ion exchange resin and a scavenger resin and the like.

In each of the aforementioned reactions, when the starting compound has amino, carboxy, hydroxy or carbonyl as a substituent, these groups may have a protecting group introduced therein, such as one generally used in peptide chemistry and the like. The objective compound can be obtained by removing the protecting group as necessary after the reaction.

As the amino-protecting group, for example, formyl, C_{1-6} alkyl-carbonyl (e.g., acetyl, propionyl and the like), C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and the like), benzoyl, C_{7-13} aralkyl-carbonyl (e.g., benzylcarbonyl and the like), C_{7-13} aralkoxy-carbonyl (e.g., benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl and the like), trityl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C_{2-6} alkenyl (e.g., 1-allyl and the like) and the like can be mentioned. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C_{1-6} alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

As the carboxy-protecting group, for example, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), C_{7-13} aralkyl (e.g., benzyl and the like), phenyl,

trityl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C₂₋₆ alkenyl (e.g., 1-allyl and the like) and the like can be mentioned. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

As the hydroxy-protecting group, for example, C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and the like), phenyl, trityl, C₇₋₁₃ aralkyl (e.g., benzyl and the like), formyl, C₁₋₆ alkyl-carbonyl (e.g., acetyl, propionyl and the like), benzoyl, C₇₋₁₃ aralkyl-carbonyl (e.g., benzylcarbonyl and the like), 2-tetrahydropyranyl, 2-tetrahydrofuranyl, silyl (e.g., trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl and the like), C₂₋₆ alkenyl (e.g., 1-allyl and the like) and the like can be mentioned. These groups are optionally substituted by 1 to 3 halogen atom(s) (e.g., fluorine, chlorine, bromine, iodine and the like), C₁₋₆ alkyl (e.g., methyl, ethyl, propyl and the like), C₁₋₆ alkoxy (e.g., methoxy, ethoxy, propoxy and the like) or nitro and the like.

As the carbonyl-protecting group, for example, cyclic acetal (e.g., 1,3-dioxane and the like), non-cyclic acetal (e.g., di-C₁₋₆ alkyl acetal and the like) and the like can be mentioned.

The removing method of these protecting groups may be carried out by methods known per se, for example, the methods described in *Protective Groups in Organic Synthesis*, published by John Wiley and Sons, 1980, and the like. For example, employed are the methods using acids, bases, ultraviolet ray, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g., trimethylsilyl iodide, trimethylsilyl bromide, etc.), etc.; and reduction method, and the like.

When the starting compound can form a salt in each of the aforementioned reactions, the compound may be used in the form of a salt. As such salt, for example, those exemplified for the salt of the compound represented by the formula (I) can be used.

Where the compound (I) includes optical isomers, stereoisomers, regioisomers and rotational isomers, those are also encompassed in the compound (I), and can be obtained as a single compound by synthetic methods and separation methods known per se. For example, when optical isomers of the compound (I) exist, optical isomers resolved from the compound are also encompassed in the compound (I).

The optical isomers can be produced by a method known per se. Concretely, an optically active isomer can be obtained using an optically active synthetic intermediate or by optical resolution of a final racemate by a conventional method.

For optical resolution, a method known per se, such as a fractional recrystallization method, a chiral column method, a diastereomer method, and the like can be used.

1) Fractional Recrystallization Method

The method which comprises allowing a racemate and an optically-active compound (e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.) to form a salt, which is then separated through fractional recrystallization method, followed by, when desired, subjecting the salt to a neutralization step to give a free optical isomer.

2) Chiral Column Method

The method of separating by applying a racemate or a salt thereof, to a column for fractionating optical isomers (chiral column). In the case of, for example, liquid chromatography, the optical isomers are separated by applying a mixture of optical isomers to a chiral column, such as ENANTIO-OVM (manufactured by Tosoh Corp.), CHIRAL SERIES (manufactured by Daicel Co.), etc., and developing with water, various buffers (e.g., phosphate buffer) and organic solvents (e.g., ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.), singly or as a suitable mixture of them. In the case of, for example, gas chromatography, a chiral column such as CP-Chirasil-DeX CB (manufactured by GL Science Co.), etc. is used for separation.

3) Diastereomer Method

The method that a racemic mixture is chemically reacted with an optically-active reagent to give a mixture of diastereomers, which is subjected to an ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to give a single compound, which is then subjected to a chemical treatment (e.g., hydrolysis reaction etc.) to separate the optically-active reagent site from the compound to give an optical isomer. For example, where compound (I) has a hydroxy or a primary or secondary amino in the molecule, the compound and an optically-active organic acid (e.g., MTPA [α -methoxy- α -(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid, etc.) or the like are subjected to condensation reaction to give the respectively corresponding ester or amide diastereomer. On the other hand, where compound (I) has a carboxylic acid group, the compound and an optically-active amine or alcohol reagent are subjected to condensation reaction to give an amide or ester diastereomer. The separated diastereomer is then subjected to acidic or basic hydrolysis reaction, through which it is converted into the optical isomer of the original compound.

The present invention is explained in detail in the following by referring to Reference Examples, Examples, Experimental Examples and Formulation Examples, which are not to be construed as limitative.

In the following Reference Examples and Examples, “%” means percent by weight unless specifically indicated. In addition, room temperature means a temperature of 1–30° C.

EXAMPLES

Reference Example 1

Ethyl 2-chloro-4-isopropyl-5-thiazolecarboxylate (30.0 g) was dissolved in toluene (200 mL) and to the solution was added dropwise a 70% solution (59.1 g) of sodium dihydrido bis(2-methoxyethoxy)aluminate in toluene at 0° C. To the reaction mixture was added a 10% aqueous solution (100 mL) of potassium sodium tartrate tetrahydrate, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated to give a yellow oil (23.2 g). This oil was dissolved in tetrahydrofuran (150 mL) and manganese dioxide (60 g) was added, and the mixture was stirred at room temperature for 12 hrs. Manganese dioxide was removed by filtration and the organic layer was concentrated. The residue was purified by silica gel column chromatography. 2-Chloro-4-isopropyl-5-thiazolecarbaldehyde (12.0 g, 54%) was obtained as a yellow oil from a fraction eluted with hexane-ethyl acetate (9:1, volume ratio).

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NMR(CDCl₃) delta:1.39(6H,t,d,J=7 Hz),3.45–3.65(1H,m),10.06(1H,s).

In the same manner as in Reference Example 1 except that an ethyl 2-chloro-5-thiazolecarboxylate derivative having a different substituent at the 4-position was used as a starting material, the compound of Reference Example 2–4 was synthesized.

Reference Example 2

4-tert-butyl-2-chloro-5-thiazolecarbaldehyde

yield: 69%. a yellow oil. NMR(CDCl₃) delta: 1.52(9H,s),10.31(1H,s).

Reference Example 3

2-chloro-4-phenyl-5-thiazolecarbaldehyde

yield 70%. pale-yellow solid

Reference Example 4

2-chloro-4-methyl-5-thiazolecarbaldehyde yield 82%. a yellow oil. NMR(CDCl₃) delta: 2.31(3H,s),10.31(1H,s).

Reference Example 5

A mixture of 2-chloro-4-isopropyl-5-thiazolecarbaldehyde (2.0 g), ethyl diethylphosphonoacetate (2.47 g), sodium hydride (0.44 g) and N,N-dimethylformamide (10 mL) was stirred at room temperature for 1 hr. Benzimidazole (1.54 g) and sodium hydride (0.44 g) were added to the reaction mixture and the mixture was further stirred at room temperature for 1 hr. The reaction mixture was poured into water, the precipitated crystals were collected by filtration and washed with water. Recrystallization from acetone-hexane gave ethyl (2E)-3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]propenoate (3.01 g, 84%) as a pale-yellow prism crystal. melting point: 229–230° C.

In the same manner as in Reference Example 5, the compounds of Reference Examples 6–8 were synthesized.

Reference Example 6

ethyl (2E)-3-[2-(1H-benzimidazol-1-yl)-4-tert-butyl-5-thiazolyl]propenoate

yield: 84%. pale-yellow prism crystal, melting point: 129–130° C. (recrystallized from acetone-hexane).

Reference Example 7

ethyl (2E)-3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-thiazolyl]propenoate

yield: 84%. amorphous solid NMR(CDCl₃) delta: 1.33(3H,t,J=7 Hz), 4.27(2H,q,J=7 Hz), 6.25(1H,d,J=15 Hz), 7.4–7.6(6H,m), 7.7–7.9(2H,m), 7.95(1H,d,J=15 Hz), 8.1–8.2(1H,m), 8.63(1H,s).

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Reference Example 8

ethyl (2E)-3-[2-(1H-benzimidazol-1-yl)-4-methyl-5-thiazolyl]propenoate

yield: 81%. pale-yellow prism crystal, melting point: 109–112° C. (recrystallized from acetone-hexane).

Reference Example 9

A mixture of ethyl (2E)-3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]propenoate (1.50 g), 5% palladium-carbon (1.0 g), tetrahydrofuran (20 mL) and ethanol (20 mL) was stirred at room temperature under an atmospheric pressure of hydrogen for 14 hrs. The catalyst was removed by filtration, and the organic layer was concentrated to give ethyl 3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]propionate (1.50 g, 99%) as a yellow oil.

NMR(CDCl₃) delta: 1.24(3H,t,J=7 Hz), 1.34(6H,d,J=7 Hz), 2.66(2H,t,J=7 Hz), 3.1–3.2(1H,m), 3.14(2H,t,J=7 Hz), 4.18(2H,q,J=7 Hz), 7.35–7.5(2H,m), 7.8–7.9(1H,m), 8.05–8.15(1H,m), 8.46(1H,s).

In the same manner as in Reference Example 9, the compounds of Reference Examples 10 and 11 were synthesized.

Reference Example 10

ethyl 3-[2-(1H-benzimidazol-1-yl)-4-tert-butyl-5-thiazolyl]propionate

yield: 99%. a yellow oil. NMR(CDCl₃) delta:1.29(3H,t,J=7 Hz), 1.48(9H,s), 2.71(2H,t,J=7 Hz), 3.32(2H,t,J=7 Hz), 4.19(2H,q,J=7 Hz), 7.3–7.5(2H,m), 7.8–7.9(1H,m), 8.05–8.15(1H,m), 8.43(1H,s).

Reference Example 11

ethyl 3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-thiazolyl]propionate

yield: 88%. pale-yellow prism crystal, melting point: 81–82° C. (recrystallized from acetone-hexane).

Reference Example 12

A mixture of methyl 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionate (1.50 g), dihydroxyphenylborane (650 mg), sodium hydrogen carbonate (1.68 g), tetrakis(triphenylphosphine)palladium (250 mg), toluene (50 mL), ethanol (25 mL) and water (25 mL) was stirred under an argon atmosphere with heating under reflux for 12 hrs. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography. Methyl 3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propionate (1.50 g, 88%) was obtained as a yellow oil from a fraction eluted with hexane-ethyl acetate (6:1, volume ratio).

NMR(CDCl₃) delta:2.82(2H,t,J=7.5 Hz), 3.29(2H,t,J=7.5 Hz), 3.70(3H,s), 7.3–7.5(5H,m), 7.69(2H,d,J=8.5 Hz), 8.0–8.1(2H,m).

In the same manner as in Reference Example 12, the compounds of Reference Examples 13–15 were synthesized.

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Reference Example 13

ethyl 4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]
butanoate

yield: 90%. a yellow oil

NMR(CDCl₃) delta: 1.24(3H,t,J=7 Hz), 2.0–2.3(2H,m),
2.43(2H,t,J=7 Hz), 3.00(2H,t,J=7 Hz), 4.12(2H,q,J=7 Hz),
7.3–7.5(5H,m), 7.66(2H,d,J=8.5 Hz), 8.0–8.1(2H,m).

Reference Example 14

methyl 3-[4-(3,4-dichlorophenyl)-2-phenyl-5-ox-
azolyl]propionate

yield: 69%. a yellow oil NMR(CDCl₃) delta: 2.83 (2H,t,
J=7 Hz), 3.29 (2H,t,J=7 Hz), 3.71 (3H,s), 7.4–7.7(5H,m),
7.91 (1H,d,J=2 Hz), 8.0–8.1 (2H,m).

Reference Example 15

methyl 6-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]
hexanoate

yield: 90%. a yellow oil NMR(CDCl₃) delta: 1.4–1.6
(2H,m), 1.6–1.9 (4H,m), 2.33 (2H,t,J=7 Hz), 2.93 (2H,t,J=7
Hz), 3.66 (3H,s), 7.4–7.5 (5H,m), 7.65 (2H,d,J=8.5 Hz),
8.0–8.1 (2H,m).

Reference Example 16

A mixture of ethyl 5-[2-chloro-4-chlorophenyl-5-ox-
azolyl]pentanoate (6.30 g), potassium carbonate (5.08 g),
benzimidazole (4.34 g) and N,N-dimethylformamide (50
mL) was stirred at 120° C. for 1 hr. The reaction mixture was
poured into water. The precipitated crystals were collected
by filtration, washed with water and dried to give ethyl
5-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-ox-
azolyl]pentanoate (7.20 g, yield 90%).

NMR(CDCl₃) delta: 1.25 (3H,t,J=7 Hz), 1.7–2.0 (4H,m),
2.39 (2H,t,J=7 Hz), 3.00 (2H,t,J=7 Hz), 4.14 (2H,q,J=7 Hz),
7.4–7.5(4H,m), 7.67(2H,d,J=8.5 Hz), 7.88 (1H,d,J=7.5 Hz),
8.26 (1H,d,J=7.5 Hz), 8.59(1H,s).

In the same manner as in Reference Example 16, the
compounds of Reference Examples 17–21 were synthesized.

Reference Example 17

methyl 3-[2-(1H-benzimidazol-1-yl)-4-(3,4-dichlo-
rophenyl)-5-oxazolyl]propionate

yield: 62%. pale-yellow prism crystal, melting point:
81–82° C. (recrystallized from acetone-isopropyl ether).

Reference Example 18

ethyl 4-[4-(4-chlorophenyl)-2-(5,6-dimethyl-1H-
benzimidazol-1-yl)-5-oxazolyl]butanoate

yield: 90%. pale-yellow prism crystal, melting point:
119–120° C. (recrystallized from acetone-hexane).

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Reference Example 19

methyl 3-[4-(4-chlorophenyl)-2-(5,6-dimethyl-1H-
benzimidazol-1-yl)-5-oxazolyl]propionate

yield: 88%. pale-yellow prism crystal, melting point:
151–152° C. (recrystallized from acetone-ethyl acetate).

Reference Example 20

ethyl 4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophe-
nyl)-5-thiazolyl]butanoate

yield: 55%. pale-yellow solid.

NMR(CDCl₃) delta: 1.26(3H,t,J=7 Hz), 2.0–2.2(2H,m),
2.42(2H,t,J=7 Hz), 3.05(2H,t,J=7 Hz), 4.13(2H,q,J=7 Hz),
7.4–7.5(4H,m), 7.64(2H,d,J=8.5 Hz), 7.85–7.9(1H,m),
8.05–8.1 (1H,m), 8.54 (1H,s).

Reference Example 21

ethyl 3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophe-
nyl)-5-thiazolyl]propionate

yield: 33%. pale-yellow prism crystal, melting point:
121–122° C. (recrystallized from acetone-ethyl acetate).

Reference Example 22

A mixture of ethyl 2-[2-chloro-4-chlorophenyl-5-ox-
azolyl]-2-oxoacetate (5.0 g), benzimidazole (2.26 g),
sodium hydride (0.76 g) and N,N-dimethylformamide (50
mL) was stirred at 0° C. for 1 hr. The reaction mixture was
poured into water, and the mixture was extracted with ethyl
acetate, washed with water, dried over anhydrous magne-
sium sulfate, and concentrated to give ethyl 2-[2-(1H-ben-
zimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-2-oxoac-
etate (4.57 g, 73%) as crystals. Recrystallization from ethyl
acetate-isopropyl ether gave pale-yellow prism crystals.
melting point: 143–144° C.

Reference Example 23

Ethyl 2-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-
5-oxazolyl]-2-oxoacetate (3.50 g) was dissolved in a mixed
solvent of tetrahydrofuran (60 mL)-ethanol (20 mL), sodium
borohydride (100 mg) was added at 0° C. and the mixture
was stirred at 0° C. for 1 hr. The reaction mixture was poured
into water, and the precipitated solid was collected by
filtration and dried. The obtained solid was added to thionyl
chloride (10 mL) at 0° C., and the mixture was stirred at
room temperature for 1 hr. The reaction mixture was con-
centrated and poured into 10% aqueous sodium hydrogen
carbonate solution and the mixture was extracted with ethyl
acetate. The organic layer was washed with water, dried over
anhydrous magnesium sulfate, and concentrated. The resi-
due was dissolved in acetic acid (50 mL) and zinc powder
(10 g) was added. The mixture was stirred with heating
under reflux for 30 min. Insoluble material was removed by
filtration, and the filtrate was concentrated and poured into
10% aqueous sodium hydrogen carbonate solution. The
mixture was extracted with ethyl acetate, and the organic
layer was washed with water, dried over anhydrous magne-
sium sulfate, and concentrated. The residue was purified by
silica gel column chromatography and ethyl 2-[2-(1H-ben-
zimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]acetate

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(2.07 g, 61%) was obtained as crystals from a fraction eluted with acetone-hexane (1:2, volume ratio). Recrystallization from acetone-isopropyl ether gave colorless needle crystals. melting point: 152–153° C.

Reference Example 24

A mixture of ethyl(2E)-3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]propenoate (1.00 g), 2N aqueous sodium hydroxide solution (5 mL), tetrahydrofuran (5 mL), ethanol (5 mL) was stirred at room temperature for 1 hr. The reaction mixture was poured into dilute hydrochloric acid and the precipitated solid was collected by filtration, washed with water and dried to give (2E)-3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]propenoic acid (0.90 g, 98%) as crystals. Recrystallization from acetone-hexane gave pale-yellow prism crystals. melting point: 262–264° C.

In the same manner as in Reference Example 24, the compounds of Reference Examples 25–38 were synthesized by alkaline hydrolysis of the corresponding ester.

Reference Example 25

(2E)-3-[2-(1H-benzimidazol-1-yl)-4-tert-butyl-5-thiazolyl]propenoic acid

yield: 93%. pale-yellow prism crystal, melting point: 256–257° C. (recrystallized from acetone-hexane).

Reference Example 26

(2E)-3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-thiazolyl]propenoic acid

yield: 89%. pale-yellow prism crystal, melting point: dec. 285° C. (recrystallized from acetone-hexane)

Reference Example 27

(2E)-3-[2-(1H-benzimidazol-1-yl)-4-methyl-5-thiazolyl]propenoic acid

yield: 81%. pale-yellow prism crystal, melting point: 247–251° C. (recrystallized from acetone-hexane).

Reference Example 28

3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]propionic acid

yield: 88%. pale-yellow prism crystal, melting point: 187–188° C. (recrystallized from acetone-hexane).

Reference Example 29

3-[2-(1H-benzimidazol-1-yl)-4-tert-butyl-5-thiazolyl]propionic acid

yield: 85%. pale-yellow prism crystal, melting point: 193–194° C. (recrystallized from acetone-hexane).

Reference Example 30

3-[2-(1H-benzimidazol-1-yl)-4-methyl-5-thiazolyl]propionic acid

yield: 82%. pale-yellow prism crystal, melting point: 175–179° C. (recrystallized from acetone-hexane).

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Reference Example 31

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]propionic acid

yield: 85%. pale-yellow prism crystal, melting point: 300° C. or above (recrystallized from acetone-hexane).

Reference Example 32

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]butanoic acid

yield: 71%. pale-yellow prism crystal, melting point: 199–200° C. (recrystallized from acetone-hexane).

Reference Example 33

2-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]acetic acid

yield: 82%. colorless needle crystal, melting point: 256–257° C. (recrystallized from methanol-ethyl acetate).

Reference Example 34

3-[4-(4-chlorophenyl)-2-(5,6-dimethyl-1H-benzimidazol-1-yl)-5-oxazolyl]propionic acid

yield: 80%. colorless needle crystal, melting point: 238–240° C. (recrystallized from ethanol-hexane).

Reference Example 35

4-[4-(4-chlorophenyl)-2-(5,6-dimethyl-1H-benzimidazol-1-yl)-5-oxazolyl]butanoic acid

yield: 97%. colorless needle crystal, melting point: 205–206° C. (recrystallized from tetrahydrofuran-hexane).

Reference Example 36

4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]butanoic acid

yield: 87%. colorless prism crystal, melting point: 158–159° C. (recrystallized from ethyl acetate-hexane).

Reference Example 37

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propionic acid

yield: 80%. colorless prism crystal, melting point: 166–167° C. (recrystallized from ethyl acetate-hexane).

Reference Example 38

5-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]pentanoic acid

yield: 93%. pale-yellow solid. NMR(CDCl₃) delta: 1.7–2.0(4H,m), 2.46 (2H,t,J=7 Hz), 3.01(2H,t,J=7 Hz), 7.2–7.3(4H,m), 7.68(2H,d,J=8.5 Hz), 7.87(1H,d,J=7.5 Hz), 8.27(1H,d,J=7.5 Hz), 8.63(1H,s).

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Reference Example 39

A mixture of 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]butanoic acid (2.03 g), potassium carbonate (2.76 g), benzimidazole (1.18 g) and N,N-dimethylformamide (30 mL) was stirred at 120° C. for 4 hrs. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration, washed with water and dried to give 4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]butanoic acid (2.22 g, yield 82%). Recrystallization from tetrahydrofuran-ethanol gave colorless needle crystals. melting point: 199–200° C.

Reference Example 40

In the same manner as in Reference Example 39, 6-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]hexanoic acid was produced.

yield: 86%. pale-yellow prism crystal, melting point: 158–159° C. (recrystallized from acetone-isopropyl ether).

Reference Example 41

A mixture of 2-bromo-4'-chloropropiophenone (45.0 g), thiobenzamide (24.7 g), sodium acetate (14.8 g) and ethanol (400 mL) was stirred with heating under reflux for 3 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated to give 4-(4-chlorophenyl)-5-methyl-2-phenylthiazole (35.1 g, 68%) as crystals. Recrystallization from ethyl acetate-hexane gave colorless prism crystals. melting point: 90–91° C.

Reference Example 42

A mixture of 4-(4-chlorophenyl)-5-methyl-2-phenylthiazole (35.1 g), N-bromosuccinimide (24.0 g), azobisisobutyronitrile (4.11 g) and carbon tetrachloride (400 mL) was stirred with heating under reflux for 3 hrs. The precipitated solid was removed by filtration and the organic layer was concentrated. The residue was purified by silica gel column chromatography. 5-(Bromomethyl)-4-(4-chlorophenyl)-2-phenylthiazole (30.8 g, 69%) was obtained as crystals from a fraction eluted with hexane-ethyl acetate (19:1, volume ratio). Recrystallization from ethyl acetate gave colorless prism crystals. melting point: 108–109° C.

Reference Example 43

To a solution of ethyl malonate (17.5 g) in N,N-dimethylformamide (50 mL) was added sodium hydride (4.38 g) and the mixture was stirred at 0° C. for 30 min, after which a solution of 5-(bromomethyl)-4-(4-chlorophenyl)-2-phenylthiazole (8.0 g) in N,N-dimethylformamide (200 mL) was added at 0° C. The mixture was stirred at 0° C. for 2 hrs. and poured into dilute hydrochloric acid. The mixture was extracted with ethyl acetate and the organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated to give a yellow oil. This oil was dissolved in ethanol (140 mL) and 10% aqueous sodium hydroxide solution (140 mL) was added. The mixture was stirred at 60° C. for 2 hrs. and the reaction mixture was poured into water. The mixture was washed with diethyl ether and the aqueous layer was acidified with dilute hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic layer was washed with saturated brine, dried over anhydrous

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magnesium sulfate and concentrated to give a yellow powder. This powder was dissolved in pyridine (140 mL) and the mixture was stirred at 100° C. for 2 hrs. The reaction mixture was concentrated and diluted with dilute hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated to give 3-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]propionic acid (5.71 g, 75%) as a yellow powder. Recrystallization from ethyl acetate-hexane gave colorless prism crystals, melting point: 142–143° C.

Reference Example 44

A mixture of methyl 3-{2-chloro-4-[4-(trifluoromethyl)phenyl-5-oxazolyl]}propionate (1.33 g), potassium carbonate (1.38 g), benzimidazole (1.18 g) and N-methylpyrrolidone (10 mL) was stirred at 120° C. for 1 hr. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration, washed with water, dried and recrystallized from ethyl acetate-hexane to give methyl 3-{2-(1H-benzimidazol-1-yl)-4-[4-(trifluoromethyl)phenyl]-5-oxazolyl}propionate (1.15 g, yield 70%) as pale-yellow prism crystals. melting point: 129–130° C.

Reference Example 45

A mixture of methyl 3-{2-(1H-benzimidazol-1-yl)-4-[4-(trifluoromethyl)phenyl]-5-oxazolyl}propionate (1.00 g), 1N aqueous sodium hydroxide solution (10 mL), tetrahydrofuran (10 mL) and ethanol (10 mL) was stirred at room temperature for 1 hr. The reaction mixture was poured into dilute hydrochloric acid, and the precipitated crystals were collected by filtration, washed with water, dried and recrystallized from tetrahydrofuran-ethanol to give 3-{2-(1H-benzimidazol-1-yl)-4-[4-(trifluoromethyl)phenyl]-5-oxazolyl}propionic acid (1.00 g, yield 83%) as pale-yellow prism crystals. melting point: 224–226° C.

Reference Example 46

To a mixture of 2-(ethylsulfanyl)ethylamine (0.94 g) and tetrahydrofuran (10 mL) was added dropwise di-tert-butyl dicarbonate (2.14 g) with stirring under ice-cooling. The mixture was stirred at room temperature for 30 min and the reaction mixture was concentrated, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated and the residue was subjected to silica gel column chromatography. tert-Butyl 2-(ethylsulfanyl)ethylcarbamate was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). (1.83 g, yield 100%).

NMR(CDCl₃) delta: 1.26(3H, t, J=7.5 Hz), 1.45(9H, s), 2.55(2H, q, J=7.5 Hz), 2.66(2H, t, J=6.5 Hz), 3.24–3.36(2H, m), 4.94(1H, brs).

Reference Example 47

To a mixture of tert-butyl 2-(ethylsulfanyl)ethylcarbamate (1.83 g) and tetrahydrofuran (15 mL) was added m-chloroperbenzoic acid (4.84 g) with stirring under ice-cooling. The reaction mixture was diluted with ethyl acetate and washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give tert-butyl 2-(ethylsulfonyl)ethylcarbamate as a colorless oil. (2.07 g, yield 98%).

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MR (CDCl₃) delta:1.42(3H, t, J=8 Hz), 1.45(9H, s), 3.04(2H, q, J=8 Hz), 3.19(2H, t, J=6.5 Hz), 3.58–3.70(2H, m), 5.22(1H, brs).

Reference Example 48

To a mixture of tert-butyl 2-(ethylsulfonyl)ethylcarbamate (1.5 g) and ethyl acetate (15 mL) was added dropwise 4N hydrochloric acid•ethyl acetate solution (4 mL) with stirring under ice-cooling. The mixture was stirred at room temperature for 4 hrs., and the precipitated crystals were collected by filtration and washed with ethyl acetate to give 2-(ethylsulfonyl)ethylamine hydrochloride as crystals. (0.76 g, yield 69%). Recrystallization from ethanol gave colorless prism crystals. melting point: 103–104° C.

Reference Example 49

To a mixture of 2-(methylsulfonyl)ethylamine (3.01 g) and tetrahydrofuran (30 mL) was added dropwise di-tert-butyl dicarbonate (8.16 g) with stirring under ice-cooling. After stirring at room temperature for 30 min, the reaction mixture was concentrated, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography and tert-butyl 2-(methylsulfonyl)ethylcarbamate (5.62 g, 89%) was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

NMR(CDCl₃) delta:1.45(9H, s), 2.11(3H, s), 2.62(2H, t, J=6.5 Hz), 3.33(2H, q, J=6.5 Hz), 4.94(1H, brs).

Reference Example 50

To a mixture of tert-butyl 2-(methylsulfonyl)ethylcarbamate (2.0 g) and tetrahydrofuran (20 mL) was added m-chloroperbenzoic acid (5.67 g) with stirring under ice-cooling. The reaction mixture was diluted with ethyl acetate and washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate, and concentrated to give tert-butyl 2-(methylsulfonyl)ethylcarbamate as crystals. The crystals were recrystallized from ethyl acetate-hexane to give colorless prism crystals. (1.78 g, yield 76%). melting point: 85–86° C.

Reference Example 51

To a mixture of tert-butyl 2-(methylsulfonyl)ethylcarbamate (1.5 g) and ethyl acetate (10 mL) was added dropwise 4N hydrochloric acid.ethyl acetate solution (3 mL) with stirring under ice-cooling. After stirring at room temperature overnight, the precipitated crystals were collected by filtration and washed with ethyl acetate to give 2-(methylsulfonyl)ethylamine hydrochloride as crystals (1.04 g, yield 97%). Recrystallization from ethanol gave colorless prism crystal. melting point: 169–170° C.

Reference Example 52

To a mixture of tert-butyl 2-(methylsulfonyl)ethylcarbamate (3.5 g) and tetrahydrofuran (20 mL) was added lithium aluminum hydride (1.39 g) with stirring under ice-cooling and the mixture was heated under reflux for 2 hrs. After cooling the reaction mixture, sodium sulfate 10 hydrate (5 g) was added, and the solid was filtered off. The filtrate was concentrated and diluted with tetrahydrofuran, and di-tert-

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butyl dicarbonate was added dropwise with stirring under ice-cooling. After stirring at room temperature for 30 min, the reaction mixture was concentrated, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and tert-butyl N-methyl-N-[2-(methylsulfonyl)ethyl]carbamate was obtained as a colorless oil (0.82 g, yield 22%) from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

NMR(CDCl₃) delta:1.46(9H, s), 2.14(3H, s), 2.56–2.68 (2H, m), 2.89(3H, s), 3.34–3.46(2H, m).

Reference Example 53

To a mixture of tert-butyl N-methyl-N-[2-(methylsulfonyl)ethyl]carbamate (0.8 g) and tetrahydrofuran (10 mL) was added m-chloroperbenzoic acid (2.11 g) with stirring under ice-cooling. The reaction mixture was diluted with ethyl acetate and washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated brine.

The organic layer was dried over anhydrous magnesium sulfate to give tert-butyl N-methyl-N-[2-(methylsulfonyl)ethyl]carbamate as a colorless oil. (0.83 g, yield 89%).

NMR(CDCl₃) delta:1.47(9H, s), 2.93(3H, s), 2.94(3H, s), 3.20–3.36(2H, m), 3.64–3.74(2H, m).

Reference Example 54

To a mixture of tert-butyl N-methyl-N-[2-(methylsulfonyl)ethyl]carbamate (0.81 g) and ethyl acetate (10 mL) was added dropwise a 4N hydrochloric acid.ethyl acetate solution (2 mL) with stirring under ice-cooling. After stirring at room temperature overnight, the precipitated crystals were collected by filtration and washed with ethyl acetate to give N-methyl-N-[2-(methylsulfonyl)ethyl]amine hydrochloride as crystals (0.38 g, yield 64%). Recrystallization from ethanol gave colorless prism crystals. melting point: 259–260° C.

Reference Example 55

To a mixture of tetrahydrothiopyran-4-one (5.0 g), hydroxylamine hydrochloride (15 g) and ethanol (400 mL) was added sodium acetate (29.3 g) and the mixture was stirred overnight at room temperature. The reaction mixture was cooled to 0° C., and the precipitated crystals were collected by filtration and washed with water at 0° C. to give tetrahydrothiopyran-4-one oxime as crystals. Recrystallization from petroleum ether gave white prism crystals. (2.36 g, yield 66%). melting point: 85–86° C.

Reference Example 56

To a mixture of lithium aluminum hydride (5.42 g) and tetrahydrofuran (400 mL) was added a solution of tetrahydrothiopyran-4-one oxime (3.75 g) in tetrahydrofuran (30 mL) with stirring under ice-cooling, and the mixture was stirred with heating under reflux overnight. After cooling the reaction mixture, a 2N aqueous sodium hydroxide solution was added, and the precipitated solid was filtered off. The filtrate was concentrated until the liquid amount became half, and di-tert-butyl dicarbonate (7.5 g) was added dropwise with stirring under ice-cooling. The mixture was stirred at room temperature for 2 hrs., and the reaction mixture was concentrated, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magne-

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sium sulfate and concentrated to give tert-butyl(tetrahydrothiopyran-4-yl)carbamate as crystals (4.68 g, yield 75%). Recrystallization from ethyl acetate-hexane gave white prism crystals. melting point: 141–142° C.

Reference Example 57

To a mixture of tert-butyl(tetrahydrothiopyran-4-yl)carbamate (2.0 g) and tetrahydrofuran (20 mL) was added m-chloroperbenzoic acid (5.0 g) with stirring under ice-cooling. The reaction mixture was diluted with ethyl acetate, and washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give tert-butyl(1,1-dioxidetetrahydro-2H-thiopyran-4-yl)carbamate as crystals (1.63 g, yield 71%). Recrystallization from diisopropyl ether-hexane gave white prism crystals. melting point: 207–208° C.

Reference Example 58

To a mixture of tert-butyl(1,1-dioxidetetrahydrothiopyran-4-yl)carbamate (1.5 g) and ethyl acetate (10 mL) was added dropwise a 4N hydrochloric acid.ethyl acetate solution (3 mL) with stirring under ice-cooling. After stirring at room temperature overnight, the precipitated crystals were collected by filtration and washed with ethyl acetate to give (1,1-dioxidetetrahydrothiopyran-4-yl)amine hydrochloride as crystals (0.78 g, yield 95%). Recrystallization from ethanol gave colorless prism crystals. melting point: 288–289° C.

Reference Example 59

To a mixture of tert-butyl 4-hydroxypiperidine-1-carboxylate (10 g) and tetrahydrofuran (100 mL) were successively added methanesulfonyl chloride (5.98 g) and triethylamine (5.53 g) at 0° C. The mixture was stirred at room temperature for 2 hrs., and the reaction mixture was diluted with ethyl acetate and washed successively with 1N aqueous sodium hydroxide solution, water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give tert-butyl 4-(methylsulfonyl)oxypiperidine-1-carboxylate as crystals. Recrystallization from ethyl acetate-hexane gave white prism crystals (13.2 g, yield 95%). melting point: 94–95° C.

Reference Example 60

A mixture of tert-butyl 4-(methylsulfonyl)oxypiperidine-1-carboxylate (12.5 g), methylmercaptan sodium salt (3.31 g), tetra-n-butylammonium iodide (1.66 g) and tetrahydrofuran (50 mL) was stirred at room temperature for 72 hrs. The insoluble material was filtered through celite and the filtrate was concentrated. The residue was subjected to silica gel column chromatography, and tert-butyl 4-(methylthio)piperidine-1-carboxylate was obtained as a colorless oil from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio) (6.89 g, yield 67%).

NMR (CDCl₃) delta: 1.45(9H, s), 1.40–1.60(2H, m), 1.82–2.00 (2H, m), 2.10(3H, s), 2.60–2.80(1H, m), 2.80–3.00 (2H, m), 3.92–4.08(2H, m).

Reference Example 61

To a mixture of tert-butyl 4-(methylthio)piperidine-1-carboxylate (3.0 g) and tetrahydrofuran (30 mL) was added

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m-chloroperbenzoic acid (7.03 g) with stirring under ice-cooling. The reaction mixture was stirred at room temperature for 6 hrs., diluted with ethyl acetate, and washed successively with 2N aqueous sodium hydroxide solution, water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate to give tert-butyl 4-(methylsulfonyl)piperidine-1-carboxylate as crystals (2.00 g, yield 59%). Recrystallization from ethyl acetate-hexane gave colorless prism crystals. melting point: 107–108° C.

Reference Example 62

To a mixture of tert-butyl 4-(methylsulfonyl)piperidine-1-carboxylate (1.5 g) and ethyl acetate (10 mL) was added dropwise a 4N hydrochloric acid.ethyl acetate solution (2.5 mL) with stirring under ice-cooling. After stirring overnight at room temperature, the precipitated crystals were collected by filtration and washed with ethyl acetate to give 4-(methylsulfonyl)piperidine hydrochloride as crystals (1.08 g, yield 95%). Recrystallization from ethanol gave colorless prism crystals. melting point: 271–272° C.

Reference Example 63

To a mixture of tetrahydrothiopyran-4-one (5.14 g) and conc. hydrochloric acid (20 mL) was added sodium azide (4.31 g) under ice-cooling. The reaction mixture was stirred at room temperature for 4 hrs., and sodium carbonate was added. The mixture was diluted with iced water and extracted with chloroform. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated to give 1,4-thiazepan-5-one as crystals (3.62 g, yield 62%). Recrystallization from ethyl acetate-hexane gave colorless prism crystals. melting point: 120–121° C.

Reference Example 64

To a mixture of lithium aluminum hydride (2.31 g) and tetrahydrofuran (100 mL) was added a solution of 1,4-thiazepan-5-one (4.0 g) in tetrahydrofuran (30 mL) with stirring under ice-cooling and the mixture was stirred at room temperature for 30 min. 2N Sodium hydroxide was added to the reaction mixture until aluminum hydroxide precipitated, and the solid was filtered off. The filtrate was concentrated until the liquid amount became half, and di-tert-butyl dicarbonate (7.32 g) was added dropwise with stirring under ice-cooling. The mixture was stirred at room temperature for 2 hrs., and the reaction mixture was concentrated, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and tert-butyl 1,4-thiazepan-4-carboxylate was obtained as a colorless oil (6.00 g, yield 91%) from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio).

NMR(CDCl₃) delta: 1.46 (9H, s), 1.92–2.10 (2H, m), 2.60–2.76 (4H, m), 3.50–3.68 (4H, m).

Reference Example 65

To a mixture of tert-butyl 1,4-thiazepan-4-carboxylate (3.0 g) and tetrahydrofuran (20 mL) was added m-chloroperbenzoic acid (7.48 g) with stirring under ice-cooling. The mixture was stirred at room temperature for 1 hr., diluted with ethyl acetate, and washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated

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brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give tert-butyl 1,1-dioxide-1,4-thiazepan-4-carboxylate as crystals (1.19 g, yield 35%). Recrystallization from ethyl acetate-hexane gave colorless prism crystals. melting point: 120–121° C.

Reference Example 66

To a mixture of tert-butyl 1,1-dioxide-1,4-thiazepan-4-carboxylate (1.0 g) and ethyl acetate (10 mL) was added dropwise a 4N hydrochloric acid.ethyl acetate solution (2.5 mL) with stirring under ice-cooling. After stirring at room temperature for 16 hrs., the precipitated crystals were collected by filtration and washed with ethyl acetate to give 1,1-dioxide-1,4-thiazepan hydrochloride as crystals (0.61 g, yield 81%). Recrystallization from ethanol gave colorless prism crystals. melting point: 196–200° C.

Reference Example 67

To a solution of 4-iodoaniline (10 g) in tetrahydrofuran (200 mL) was added di-tert-butyl dicarbonate (11 g), and the reaction mixture was heated under reflux for 16 hrs. The reaction mixture was concentrated and the residue was subjected to silica gel column chromatography, and tert-butyl 4-iodophenylcarbamate was obtained as crystals from a fraction eluted with ethyl acetate-hexane (1:4, volume ratio). Recrystallization from ethyl acetate-hexane gave colorless prism crystals (10.7 g, yield 73%). melting point: 148–149° C.

Reference Example 68

To a mixture of 4-nitrobenzaldehyde (8.56 g) and ethyl hypophosphite (7.81 g) was gradually added triethylamine (1.5 mL). After stirring for 1 hr., the reaction mixture was diluted with ethyl acetate and washed successively with 1N hydrochloric acid and water. The organic layer was dried over anhydrous magnesium sulfate, and concentrated. The residue was subjected to silica gel column chromatography, and diethyl α -hydroxy-4-nitrobenzylphosphonate was obtained as crystals from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio). Recrystallization from ethyl acetate-hexane gave yellow prism crystals (4.62 g, yield 28%). melting point: 94–95° C.

Reference Example 69

To a mixed solution of diethyl α -hydroxy-4-nitrobenzylphosphonate (1.42 g) and methanol (30 mL) was added 10% palladium-carbon (0.14 g) and the mixture was stirred at room temperature under an atmospheric hydrogen pressure for 3 hrs. Palladium-carbon was removed from the reaction mixture by filtration and the filtrate was concentrated to give diethyl 4-amino- α -hydroxybenzylphosphonate as a solid (1.02 g, yield 80%).

NMR(CDCl₃) delta: 1.18–1.34 (6H, m), 2.98 (1H, brs), 3.72 (2H, brs), 3.82–4.16 (4H, m), 4.87 (1H, d, J=10 Hz), 6.68 (2H, d, J=8.5 Hz), 7.20–7.34 (2H, m).

Reference Example 70

To a mixture of diethyl α -hydroxy-4-nitrobenzylphosphonate (1.0 g) and chloroform (10 mL) was added diethylaminosulfur trifluoride (1.4 mL) at –78° C. and the reaction mixture was warmed to room temperature. Saturated brine was added to the reaction mixture and the mixture was

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extracted with ethyl acetate. The extract was concentrated and the residue was purified by preparative HPLC to give 4-[(diethylphosphono)(fluoro)methyl]nitrobenzene (0.1 g, yield 10%) as yellow oil.

NMR(CDCl₃) delta: 1.22–1.42 (6H, m), 4.00–4.34 (4H, m), 5.86 (1H, dd, J=45, 9 Hz), 7.64 (2H, d, J=7 Hz), 8.28 (2H, d, J=9 Hz).

Reference Example 71

A mixed solution of 4-nitrobenzaldehyde (2.0 g), trimethyl orthoformate (2 mL), p-toluenesulfonic acid (20 mg) and methanol (20 mL) was heated under reflux for 30 min. The reaction mixture was concentrated, diluted with ethyl acetate, and washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated. Triethyl hypophosphite (2.12 g) and dichloromethane (30 mL) were added to the residue and a boron trifluoride diethyl ether complex (5.2 mL) was gradually added under an argon atmosphere at –20° C. The mixture was stirred overnight at room temperature. Saturated aqueous sodium hydrogen carbonate was added to the reaction mixture and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and diethyl α -methoxy-4-nitrobenzylphosphonate (3.8 g, yield 95%) was obtained as a yellow oil from a fraction eluted with ethyl acetate.

NMR(CDCl₃) delta: 1.20–1.30 (6H, m), 3.45 (3H, s), 4.02–4.20 (4H, m), 4.63 (1H, d, J=17 Hz), 7.58–7.66 (2H, m), 8.24 (2H, d, J=8.8 Hz).

Reference Example 72

To a mixed solution of diethyl α -methoxy-4-nitrobenzylphosphonate (3.7 g) and methanol (50 mL) was added 10% palladium-carbon (0.5 g) and the mixture was stirred overnight at room temperature under an atmospheric hydrogen pressure. Palladium-carbon was removed by filtration and the filtrate was concentrated to give diethyl 4-amino- α -methoxybenzylphosphonate as crystals. Recrystallization from ethyl acetate-isopropyl ether gave yellow prism crystals (2.0 g, yield 60%). melting point: 100–101° C.

Reference Example 73

To a mixed solution of 1-(3-chlorophenyl)-2-hydroxyethanone (21.8 g), potassium cyanide (20.8 g) and 2-propanol (100 mL) was added acetic acid (18 mL) at room temperature. After stirring for 30 min, water was added, and the precipitated crystals were collected by filtration and recrystallized from methanol-diisopropyl ether to give 4-(3-chlorophenyl)oxazol-2(3H)-one (6.7 g, yield 41%) as a solid.

NMR(CDCl₃) delta: 7.15 (1H, s), 7.22–7.42 (4H, m), 10.54 (1H, brs).

Reference Example 74

To a solution of 4-(3-chlorophenyl)oxazol-2(3H)-one (3.31 g) and acetonitrile (15 mL) was gradually added conc. sulfuric acid (5.01 g) at 0° C. To the reaction mixture was added methyl acrylate (3.05 mL) at 0° C. and the mixture was stirred at room temperature for 5 hrs. Water was added to the reaction mixture and the mixture was extracted with

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ethyl acetate-tetrahydrofuran (1:1). The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-[4-(3-chlorophenyl)-2-oxo-2,3-dihydro-5-oxazolyl]propionate (3.0 g, 63%) was obtained as an oil from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

NMR(CDC₃) delta: 2.71 (2H, t, J=7.5 Hz), 2.98 (2H, t, J=7.5 Hz), 3.61 (3H, s), 7.24–7.50 (4H, m).

In the same manner as in Reference Example 74, the compounds of Reference Examples 75–77 were synthesized.

Reference Example 75

methyl 3-[2-oxo-4-phenyl-2,3-dihydro-5-oxazolyl]propionate

yield: 71%. colorless prism crystal melting point: 166–167° C. (recrystallized from isopropyl ether-hexane)

Reference Example 76

methyl 3-[2-oxo-4-(4-methoxyphenyl)-2,3-dihydro-5-oxazolyl]propionate

yield: 5.7g(yield: 42%)pale-yellow solid

NMR(CDC₃) delta: 2.68 (2H, t, J=7 Hz), 2.96 (2H, t, J=7 Hz), 3.68 (3H, s), 3.84 (3H, s), 7.34–7.42 (2H, m), 8.08–8.16 (2H, m)

Reference Example 77

methyl 3-[2-oxo-4-(4-fluorophenyl)-2,3-dihydro-5-oxazolyl]propionate

yield: 5.9 g(yield: 65%)solid NMR(CDC₃) delta: 2.70 (2H, t, J=7 Hz), 2.97 (2H, t, J=7 Hz), 3.68 (3H, s), 7.10–7.20 (2H, m), 7.40–7.50 (2H, m).

Reference Example 78

To a solution of methyl 3-[4-(3-chlorophenyl)-2-oxo-2,3-dihydro-5-oxazolyl]propionate (3.0 g), phosphorus oxychloride (4 mL) was gradually added pyridine (0.86 mL) at room temperature and the mixture was stirred at 90° C. for 3 hrs. The reaction mixture was cooled and acetonitrile was added. The mixture was poured into water and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-[2-chloro-4-(3-chlorophenyl)-5-oxazolyl]propionate (2.3 g, 72%) was obtained as an oil from a fraction eluted with ethyl acetate-hexane (4:1, volume ratio).

NMR(CDC₃) delta: 2.76 (2H, t, J=7.5 Hz), 3.21 (2H, t, J=7.5 Hz), 3.70 (3H, s), 7.30–7.40 (2H, m), 7.48–7.54 (1H, m), 7.66 (1H, s).

In the same manner as in Reference Example 78, the compounds of Reference Examples 79–81 were synthesized.

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Reference Example 79

ethyl 3-[2-chloro-4-phenyl-5-oxazolyl]propionate

yield: 63%. an oil

MR (CDC₃) delta: 2.74 (2H, t, J=7.5 Hz), 3.22 (2H, t, J=7.5 Hz), 3.69 (3H, s), 7.28–7.48 (3H, m), 7.58–7.66 (2H, m).

Reference Example 80

methyl 3-[2-chloro-4-(4-methoxyphenyl)-5-oxazolyl]propionate

yield: 12%. an oil NMR(CDC₃) delta: 2.73 (2H, t, J=7 Hz), 3.18 (2H, t, J=7 Hz), 3.69 (3H, s), 3.84 (3H, s), 6.90–7.00 (2H, m), 7.50–7.60 (2H, m).

Reference Example 81

methyl 3-[2-chloro-4-(4-fluorophenyl)-5-oxazolyl]propionate

yield: 72%. an oil NMR(CDC₃) delta: 2.76 (2H, t, J=7.5 Hz), 3.21 (2H, t, J=7.5 Hz), 3.70 (3H, s), 7.30–7.40 (2H, m), 7.48–7.54 (1H, m), 7.66 (1H, s).

Reference Example 82

A mixture of methyl 3-[2-chloro-4-(3-chlorophenyl)-5-oxazolyl]propionate (2.31 g), 1H-benzoimidazole (1.82 g), potassium carbonate (3.19 g) and N,N-dimethylformamide (12 mL) was stirred at 120° C. for 2 hrs. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-[2-(1H-benzoimidazol-1-yl)-4-(3-chlorophenyl)-5-oxazolyl]propionate (1.85 g, 63%) was obtained as a solid from a fraction eluted with ethyl acetate-hexane (1:1, volume ratio).

NMR(CDC₃) delta: 2.86 (2H, t, J=7 Hz), 3.36 (2H, t, J=7 Hz), 3.73 (3H, s), 7.38–7.56 (4H, m), 7.60–7.66 (1H, m), 7.76–7.82 (1H, m), 7.86–7.90(1H, m), 8.20–8.26(1H, m), 8.57(1H, s).

In the same manner as in Reference Example 82, the compounds of Reference Examples 83–85 were synthesized.

Reference Example 83

methyl 3-[2-(1H-benzoimidazol-1-yl)-4-phenyl-5-oxazolyl]propionate

yield: 72%. solid NMR(CDC₃) delta: 2.85 (2H, t, J=7.5 Hz), 3.36 (2H, t, J=7.5 Hz), 3.72(3H, s), 7.38–7.52(5H, m), 7.76(2H, d, J=7 Hz), 7.88(1H, d, J=7 Hz), 8.26(1H, d, J=7 Hz), 8.58(1H, s).

Reference Example 84

methyl 3-[2-(1H-benzoimidazol-1-yl)-4-(4-methoxyphenyl)-5-oxazolyl]propionate

yield: 61%. solid NMR(CDC₃) delta: 2.83 (2H, t, J=7.5 Hz), 3.33 (2H, t, J=7.5 Hz), 3.72 (3H, s), 3.87 (3H, s), 7.02 (2H, d, J=9 Hz), 7.38–7.50 (2H, m), 7.68 (2H, d, J=9 Hz), 7.87 (1H, d, J=8 Hz), 8.24 (1H, d, J=8 Hz), 8.57 (1H, s).

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Reference Example 85

methyl 3-[2-(1H-benzimidazol-1-yl)-4-(4-fluorophenyl)-5-oxazolyl]propionate

yield: 70%. solid NMR(CDCl₃) delta: 2.85 (2H, t, J=8 Hz), 3.33 (2H, t, J=8 Hz), 3.72 (3H, s), 7.14–7.22 (2H, m), 7.38–7.50 (2H, m), 7.70–7.80 (2H, m), 7.84–7.90 (1H, m), 8.20–8.26 (1H, m), 8.57 (1H, s).

Reference Example 86

To a mixed solution of methyl 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionate (1.5 g), 4-tert-butylphenol (0.9 g) and N,N-dimethylformamide (20 mL) was added sodium hydride (60% in oil, 0.24 g) and the mixture was stirred at room temperature for 2 hrs., and further stirred at 70° C. for 30 min. The reaction mixture was diluted with methanol (20 mL) and 2N aqueous sodium hydroxide solution (5 mL) was added. The mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water, acidified with 2N aqueous hydrochloric acid solution, and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 3-[2-(4-tert-butylphenoxy)-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (1.6 g, yield 80%) as crystals. Recrystallization from ethanol gave colorless prism crystals. melting point: 166–167° C.

Reference Example 87

A mixed solution of 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (1.43 g), cyclohexylmercaptan (0.6 g) and N,N-dimethylformamide (20 mL) was stirred at 100° C. for 1.5 hrs. The reaction mixture was diluted with water, and washed with diethyl ether. The aqueous layer was acidified with 2N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 3-[4-(4-chlorophenyl)-2-(cyclohexylsulfanyl)-5-oxazolyl]propionic acid (0.95 g, yield 52%) as crystals. Recrystallization from ethanol gave colorless prism crystals. melting point: 136–137° C.

Reference Example 88

A mixed solution of 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (1.43 g), 1-methylpiperazine (2.5 g) and isopropyl alcohol (20 mL) was heated under reflux for 10 hrs. The reaction mixture was concentrated, diluted with water, and acidified with 2N aqueous hydrochloric acid solution. The precipitated crystals were collected by filtration and recrystallized from ethanol to give 3-[4-(4-chlorophenyl)-2-(4-methyl-1-piperazinyl)-5-oxazolyl]propionic acid (1.37 g, yield 70%) as colorless prism crystals. melting point: 157–160° C.

Reference Example 89

A mixed solution of 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (1.43 g), 2-mercapto-4-methylpyrimidine hydrochloride (1.05 g), potassium carbonate (2.76 g) and N,N-dimethylformamide (20 mL) was stirred at 110° C. under a nitrogen atmosphere for 10 hrs. The reaction mixture was diluted with water, and acidified with 2N aqueous

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hydrochloric acid solution. The precipitated crystals were collected by filtration and recrystallized from methanol to give 3-[4-(4-chlorophenyl)-2-[(4-methylpyrimidin-2-yl)sulfanyl]-5-oxazolepropionic acid (1.65 g, yield 88%) as colorless prism crystals. melting point: 174–175° C.

Reference Example 90

To a mixed solution of methyl 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionate (3.0 g), imidazole (0.82 g) and N,N-dimethylformamide (20 mL) was added sodium hydride (60% in oil, 0.5 g), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was poured into iced water, and the precipitated crystals were collected by filtration to give methyl 3-[4-(4-chlorophenyl)-2-(1H-imidazol-1-yl)-5-oxazolyl]propionate (1.6 g, yield 80%) as crystals. Recrystallization from methanol gave colorless prism crystals. melting point: 95–96° C.

Reference Example 91

Methyl 3-[4-(4-chlorophenyl)-2-(1H-imidazol-1-yl)-5-oxazolyl]propionate (1.6 g) and p-formaldehyde (37% aqueous solution, 4 mL) were stirred in a sealed tube at 100° C. for 16 hrs. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-[4-(4-chlorophenyl)-2-[2-(hydroxymethyl)-1H-imidazol-1-yl]-5-oxazolyl]propionate was obtained from a fraction eluted with chloroform-ethyl acetate-methanol (8:1:4, volume ratio). 2N Aqueous sodium hydroxide solution (2 mL) and methanol (4 mL) were added to this ester form, and the mixture was stirred at 80° C. for 10 min. The reaction mixture was diluted with water and acidified with 2N aqueous hydrochloric acid solution. The precipitated crystals were collected by filtration and recrystallized from methanol-chloroform to give 3-[4-(4-chlorophenyl)-2-[2-(hydroxymethyl)-1H-imidazol-1-yl]-5-oxazolyl]propionic acid (0.65 g, yield 38%) as colorless prism crystals. melting point: 171–173° C.

Reference Example 92

To a solution of 1-propylmercaptan (0.54 mL) in methanol (20 mL) was added sodium methoxide (1.1 g) and then methyl 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionate (1.5 g) was added. The mixture was stirred with heating under reflux for 30 min. The reaction mixture was concentrated, diluted with water, and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and methyl 3-[4-(4-chlorophenyl)-2-(1-propylsulfanyl)-5-oxazolyl]propionate was obtained from a fraction eluted with hexane-acetone (9:1, volume ratio). 2N Aqueous sodium hydroxide solution (5 mL) and methanol (15 mL) were added to this ester form, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with water and acidified with 2N aqueous hydrochloric acid solution. The precipitated crystals were collected by filtration and recrystallized from isopropyl ether to give 3-[4-(4-chlorophenyl)-2-(1-propylsulfanyl)-5-oxazolyl]propionic acid (1.0 g, yield 63%) as colorless prism crystals. melting point: 128–129° C.

Reference Example 93

To a mixture of 2-(methylsulfanyl)-1H-imidazole (1.09 g), methyl 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate (2.4 g) and N,N-dimethylformamide (24 mL) was added sodium hydride (60% in oil, 0.4 g), and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated to give methyl 3-{4-(4-chlorophenyl)-2-[2-(methylsulfanyl)-1H-imidazol-1-yl]-5-oxazolyl}propionate (1.9 g, yield 63%) as crystals. Recrystallization from methanol gave pale-brown prism crystals. melting point: 88–89° C.

Reference Example 94

To a solution of methyl 3-{4-(4-chlorophenyl)-2-[2-(methylsulfanyl)-1H-imidazol-1-yl]-5-oxazolyl}propionate (2.0 g) in dichloromethane (40 mL) was added m-chloroperbenzoic acid (70% purity, 2.6 g) at 0° C. The reaction mixture was stirred at room temperature for 1 hr., washed successively with aqueous sodium sulfite solution and saturated aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated to give methyl 3-{4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl}propionate (1.65 g, yield 76%) as crystals. Recrystallization from methanol gave colorless prism crystals. melting point: 112–113° C.

Reference Example 95

To a solution of methyl 3-{4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl}propionate (1.4 g) in 1,4-dioxane (7 mL) was added 2N aqueous sodium hydroxide solution (3.5 mL) and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with water, and acidified with 2N aqueous hydrochloric acid solution. The precipitated crystals were collected by filtration and recrystallized from methanol to give 3-{4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl}propionic acid (1.22 g, yield 90%) as colorless prism crystals. melting point: 166–167° C.

Reference Example 96

A mixture of 1-(chloroacetyl)-5,6,7,8-tetrahydronaphthalene (12.0 g) and acetamide (34 g) was stirred at 135° C. for 3.5 hrs. The reaction mixture was poured into water, and saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and 2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)oxazole (9.57 g, yield 78%) was obtained as crystals from a fraction eluted with ethyl acetate-hexane (1:9, volume ratio). Recrystallization from hexane-ethyl acetate gave colorless prism crystals. melting point: 53–54° C.

Reference Example 97

To a solution of 2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)oxazole (9.0 g) in dichloromethane (90 mL) was added dropwise a solution of bromine (2.2 mL) in dichlo-

romethane (5 mL) at room temperature. After stirring the mixture at room temperature for 30 min, saturated aqueous sodium hydrogen carbonate was added, and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 5-bromo-2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)oxazole (11.7 g, yield 95%) as crystals. Recrystallization from ethanol gave colorless plate crystals. melting point: 97–98° C.

Reference Example 98

To a mixed solution of 5-bromo-2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)oxazole (11.0 g) and tetrahydrofuran (100 mL) was added dropwise a 1.6N n-butyllithium hexane solution (24 mL) at –78° C. under a nitrogen atmosphere. After stirring the reaction mixture at –78° C. for 10 min, CO₂ gas was blown into the reaction mixture for 30 min. The reaction mixture was poured into water and washed with ether. The aqueous layer was acidified with conc. hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated to give [2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]carboxylic acid (7.4 g, yield 76%) as crystals. Recrystallization from ethyl acetate gave colorless crystals. melting point: 183–185° C.

Reference Example 99

To a solution of [2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]carboxylic acid (6.0 g) in methanol (120 mL) was added conc. sulfuric acid (6.0 mL) and the mixture was stirred with heating under reflux for 18 hrs. The reaction mixture was concentrated and the residue was diluted with water. The mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate, water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated to give methyl [2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]carboxylate (4.75 g, yield 76%) as crystals. Recrystallization from ethanol gave colorless crystals. melting point: 96–97° C.

Reference Example 100

To a solution of methyl [2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]carboxylate (4.5 g) in diethyl ether (90 mL) was added lithium aluminum hydride (0.63 g) at 0° C. After stirring the reaction mixture at room temperature for 30 min, water (3.2 mL) was added, and the precipitated solid was removed by filtration. The filtrate was concentrated and the obtained solid was washed with isopropyl ether to give [2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]methanol (3.63 g, yield 90%) as crystals. Recrystallization from ethanol gave colorless crystals. melting point: 132–133° C.

Reference Example 101

To a solution of [2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]methanol (3.3 g) in (40 mL) was added thionyl chloride (1.5 mL) at 0° C. After stirring at room temperature for 15 min, the reaction mixture was concentrated. To the residue was added saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed successively

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with water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated to give an oil. To a mixed solution of 2-chloroethyl acetate (2.68 g) and N,N-dimethylformamide (40 mL) was added sodium hydride (60% in oil, 0.6 g) and the mixture was stirred at 0° C. for 5 min. To this the reaction mixture was added a solution of the aforementioned oil in N,N-dimethylformamide (10 mL) at room temperature and the mixture was stirred at room temperature for 2.5 hrs. Water was poured into the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was diluted with ethanol (30 mL) and a 2N aqueous sodium hydroxide solution (16 mL) was added at 0° C. and the mixture was stirred for 20 min. Water was added to the reaction mixture and the mixture was washed with diethyl ether. The aqueous layer was acidified with 2N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The precipitated crystals were collected by filtration and recrystallized from ethanol to give 2-chloro-3-[2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]propionic acid (3.93 g, yield 91%) as colorless prism crystals. melting point: 141–142° C.

Reference Example 102

To a solution of 2-chloro-3-[2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]propionic acid (3.2 g) in acetic acid (30 mL) was added zinc powder (3.25 g) at 90° C. and the mixture was stirred at 90° C. for 15 min. The insoluble material was removed by filtration and the filtrate was concentrated. Water was added to the residue, and the precipitated crystals were collected by filtration and recrystallized from methanol to give 3-[2-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-5-oxazolyl]propionic acid (2.25 g, yield 79%) as colorless prism crystals. melting point: 135–136° C.

Reference Example 103

A mixture of 2,4-dibromo-1-phenylbutan-1-one (30.6 g) and acetamide (47.2 g) was stirred at 130° C. for 1 hr. The reaction mixture was poured into iced water, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and 2-(2-methyl-4-phenyl-5-oxazolyl)ethyl acetate (16.6 g, yield 68%) was obtained as an oil from a fraction eluted with acetone-hexane (1:4, volume ratio). A solution of this oil (16.6 g) in methanol (40 mL) was added a 2N aqueous sodium hydroxide solution (40 mL). After stirring at room temperature for 30 min, the reaction mixture was acidified with conc. hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue (10.5 g) was dissolved in chloroform (100 mL), N,N-dimethylformamide (4 mL) was added, and thionyl chloride (11.4 mL) was added dropwise at 0° C.

After stirring with heating under reflux for 30 min, the reaction mixture was concentrated. To the residue was added saturated aqueous sodium hydrogen carbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine,

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dried over anhydrous magnesium sulfate and concentrated to give 5-(2-chloroethyl)-2-methyl-4-phenyloxazole (11.0 g, yield 97%) as an oil. This oil (9.8 g) was dissolved in acetone (150 mL) and sodium iodide (12.3 g) was added. The mixture was heated under reflux for 26 hrs. The reaction mixture was concentrated and water was added, and the mixture was extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 5-(2-iodoethyl)-2-methyl-4-phenyloxazole (11.5 g, yield 83%) as an oil. This oil (11.5 g) was dissolved in dimethyl sulfoxide (20 mL) and added dropwise to a solution of sodium cyanide (2.16 g) in dimethyl sulfoxide (80 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hrs. and iced water was added. The mixture was extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and 3-(2-methyl-4-phenyl-5-oxazolyl)propionitrile (3.3 g, yield 42%) was obtained as an oil from a fraction eluted with diethyl ether-hexane (1:1, volume ratio). To this oil (3.0 g) were added benzaldehyde (7.5 g) and zinc chloride (0.78 g), and the mixture was stirred at 170° C. for 5 hrs. The reaction mixture was cooled and water was added. The mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and 3-[4-phenyl-2-((E)-2-phenylethenyl)-5-oxazolyl]propionitrile (1.45 g, yield 34%) was obtained as crystals from a fraction eluted with diethyl ether-hexane (3:7, volume ratio). Recrystallization from methanol gave pale-brown crystals. melting point: 117–118° C.

Reference Example 104

To a solution of 3-[4-phenyl-2-((E)-2-phenylethenyl)-5-oxazolyl]propionitrile (1.3 g) in ethanol (18 mL) was added 2N aqueous sodium hydroxide solution (9 mL) and the mixture was stirred with heating under reflux for 5 hrs. The reaction mixture was cooled and water was added. The mixture was acidified with 2N aqueous hydrochloric acid solution, and extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The precipitated crystals were collected by filtration and recrystallized from ethanol to give 3-[4-phenyl-2-((E)-2-phenylethenyl)-5-oxazolyl]propionic acid (0.9 g, yield 65%) as colorless prism crystals. melting point: 138–139° C.

Reference Example 105

A mixture of 4-phenyl-2,5-dimethyloxazole (6.21 g), N-bromosuccinimide (5.34 g), azobisisobutyronitrile (0.25 g) and carbon tetrachloride (90 mL) was stirred with heating under reflux for 15 min. The reaction mixture was cooled, washed successively with water, saturated aqueous sodium hydrogen carbonate and water, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from ethanol to give 5-bromomethyl-4-phenyl-2-methyloxazole (6.73 g, yield 78%) as colorless crystals. melting point: 75–76° C.

Reference Example 106

To a solution of diethyl 2-methylmalonate acid (3.13 g) in N,N-dimethylformamide (30 mL) was added sodium

hydride (60% in oil, 0.6 g) at 0° C. and the mixture was stirred for 5 min. To the reaction mixture was added a solution of 5-bromomethyl-4-phenyl-2-methyloxazole (3.78 g) in N,N-dimethylformamide (20 mL). After stirring the reaction mixture for 30 min, iced water was added, and the mixture was extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was diluted with ethanol (15 mL) and a 2N aqueous sodium hydroxide solution (10 mL) was added at 0° C., and the mixture was further stirred for 1.5 hrs. Water was added to the reaction mixture, and the mixture was washed with diethyl ether. The aqueous layer was acidified with 2N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine (100 mL), dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in pyridine (30 mL) and the mixture was stirred with heating under reflux for 4 hrs. The reaction mixture was concentrated, dissolved in ethanol (15 mL) and 2N aqueous sodium hydroxide solution (15 mL) was added. The mixture was further stirred for 1 hr. Water was added to the reaction mixture, and the mixture was washed with diethyl ether. The aqueous layer was acidified with 2N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate.

The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The precipitated crystals were collected by filtration and recrystallized from isopropyl ether to give 2-methyl-3-(4-phenyl-2-methyl-5-oxazolyl)propionic acid (2.25 g, yield 61%) as crystals. melting point: 109–110° C.

Reference Example 107

To a solution of diisopropylamine (2.02 g) in tetrahydrofuran (20 mL) was added dropwise a 1.6N n-butyllithium hexane solution (12.5 mL) at 0° C. After stirring the reaction mixture for 10 min, a solution of isobutyric acid (0.88 g) in tetrahydrofuran (5 mL) was added. After further stirring the reaction mixture for 30 min, a solution of 5-bromomethyl-4-(4-chlorophenyl)-2-methyloxazole (2.52 g) in tetrahydrofuran (15 mL) was added. After stirring for 1 hr., water was added, and the mixture was concentrated. The residue was washed with diethyl ether. The aqueous layer was acidified with 2N aqueous hydrochloric acid solution and extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in 10% hydrochloric acid methanol solution (30 mL) and the mixture was stirred with heating under reflux for 1.5 hrs. The reaction mixture was concentrated and saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography, and an oil was obtained from a fraction eluted with diethyl ether-hexane (3:7, volume ratio).

This oil was dissolved in ethanol (5 mL) and 2N aqueous sodium hydroxide solution (5 mL) was added. The mixture was stirred at 80° C. for 15 min. The reaction mixture was acidified with 2N aqueous hydrochloric acid solution and extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The pre-

cipitated crystals were collected by filtration and recrystallized from isopropyl ether to give 2,2-dimethyl-3-(2-methyl-4-phenyl-5-oxazolyl)propionic acid (1.0 g, yield 39%) as crystals. melting point: 129–130° C.

Reference Example 108

To a solution of 1-(4-chlorophenyl)propan-1-one (6.5 g) in dichloromethane (60 mL) was added a solution of bromine (2.0 mL) in dichloromethane (5 mL) at room temperature. The reaction mixture was concentrated and 1-methylcyclohexanecarboxamide (5.44 g) was added and the mixture was stirred at 130° C. for 3 hrs. Water was added to the reaction mixture, and the mixture was extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate, concentrated and purified by silica gel column chromatography (developing solvent: acetone-hexane (1:9, volume ratio)). To the obtained oil were added iodine (7.0 g), N-bromosuccinimide (4.3 g), azobisisobutyronitrile (0.2 g) and carbon tetrachloride (70 mL) and the mixture was heated under reflux for 30 min. The solid was removed by filtration and the filtrate was concentrated to give an oil. To a mixed solution of ethyl 2-chloroacetate (1.65 g) and N,N-dimethylformamide (20 mL) was added sodium hydride (60% in oil, 0.4 g) at 0° C. and the mixture was stirred for 10 min. The aforementioned oil was added to the reaction mixture and the mixture was further stirred for 1 hr. The reaction mixture was poured into water, and extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in ethanol (10 mL) and a 2N aqueous sodium hydroxide solution (15 mL) was added. The mixture was further stirred for 1 hr. Water was added to the reaction mixture, and the mixture was washed with diethyl ether. The aqueous layer was acidified with 2N aqueous hydrochloric acid solution and extracted with diethyl ether. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was diluted with acetic acid (10 mL) and zinc powder (0.68 g) was added at 90° C. The mixture was stirred at 90° C. for 15 min. Insoluble material was removed by filtration and the filtrate was concentrated. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue purified by silica gel column chromatography (developing solvent: acetone-hexane (1:4, volume ratio)) to give 3-[4-(4-chlorophenyl)-2-(1-methylcyclohexyl)-5-oxazolyl]propionic acid (0.65 g, yield 5%) as crystals. Recrystallization from diisopropyl ether gave colorless prism crystals. melting point: 138–139° C.

Reference Example 109

A mixture of methyl 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionate (1.50 g), 1H-indazole (1.18 g), potassium carbonate (1.38 g) and N,N-dimethylformamide (20 mL) was stirred at 120° C. for 3 hrs. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated. The obtained crystals

were collected by filtration, dried and dissolved in a mixed solvent of tetrahydrofuran (20 mL) and ethanol (20 mL). A 1N aqueous sodium hydroxide solution (10 mL) was added, and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was acidified with 1N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated. The obtained crystals were collected by filtration using isopropyl ether and dried to give 3-[4-(4-chlorophenyl)-2-(1H-indazol-1-yl)-5-oxazolyl]propionic acid (824 mg, yield 45%) as pale-yellow prism crystal. melting point: 204–205° C.

Reference Example 110

A mixture of 3,4-(methylenedioxy)benzoic acid (3.24 g), oxalyl chloride (2.97 g), N,N-dimethylformamide (0.1 mL) and tetrahydrofuran (80 mL) and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated and the residue was dissolved in pyridine (50 mL). To this solution was added a solution of methyl 5-(4-chlorophenyl)-4-hydroxy-5-oxopentanoate (5.0 g) in pyridine (25 mL) at 0° C. After stirring at room temperature for 1.5 hrs., the reaction mixture was poured into a 1N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with a 1N aqueous hydrochloric acid solution, water and saturated brine, dried over anhydrous magnesium sulfate, and concentrated to give a yellow oil. This oil was dissolved in acetic acid (100 mL), and ammonium acetate (7.52 g) was added. The mixture was stirred with heating under reflux for 2 hrs. The reaction mixture was concentrated, poured into water and extracted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography and methyl 3-[4-(4-chlorophenyl)-2-[3,4-(methylenedioxy)phenyl]-5-oxazolyl]propionate (1.59 g, 21%) was obtained as a colorless powder from a fraction eluted with hexane-ethyl acetate (4:1). Recrystallization from ethanol gave colorless prism crystals. melting point: 123–124° C.

In the same manner as in Reference Example 110, the compounds of Reference Examples 111–122 were synthesized.

Reference Example 111

methyl 3-[4-(4-chlorophenyl)-2-(1-naphthyl)-5-oxazolyl]propionate

yield: 44%. colorless prism crystal. melting point: 76–77° C. (recrystallized from isopropyl ether-hexane)

Reference Example 112

methyl 3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-2-yl)-5-oxazolyl]propionate

yield: 36%. an oil NMR(CDCl₃) delta: 2.42–2.80 (4H, m), 3.70 (3H, s), 4.02 (3H, s), 6.11 (1H, dd, J=9, 4 Hz), 7.10–7.20 (1H, m), 7.32–7.40 (2H, m), 7.42–7.54 (3H, m), 7.66–7.72 (1H, m), 8.02–8.10 (2H, m).

Reference Example 113

methyl 3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propionate

yield: 36%. colorless prism crystal. melting point: 132–133° C. (recrystallized from isopropyl ether-hexane)

Reference Example 114

methyl 3-[4-(4-chlorophenyl)-2-(1H-indazol-3-yl)-5-oxazolyl]propionate

yield: 7%. colorless prism crystal. melting point: 180–181° C. (recrystallized from isopropyl ether-hexane)

Reference Example 115

methyl 3-[4-(4-chlorophenyl)-2-(2,3-dichlorophenyl)-5-oxazolyl]propionate

yield: 23%. colorless prism crystal. melting point: 92–93° C. (recrystallized from isopropyl ether-hexane)

Reference Example 116

methyl 3-[4-(4-chlorophenyl)-2-cyclohexyl-5-oxazolyl]propionate

yield: 65%. a yellow oil. NMR(CDCl₃) delta: 1.25–1.85 (8H, m), 2.05–2.1 (2H, m), 2.71 (2H, t, J=8 Hz), 3.17 (2H, t, J=8 Hz), 3.68 (3H, s), 7.37 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz).

Reference Example 117

methyl 3-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]propionate

yield: 41%. a yellow oil. NMR(CDCl₃) delta: 2.68 (2H, t, J=8 Hz), 3.15 (2H, t, J=8 Hz), 3.62 (3H, s), 4.11 (2H, s), 7.25–7.35 (5H, m), 7.37 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz).

Reference Example 118

methyl 3-[4-(4-chlorophenyl)-2-(4-fluorophenyl)-5-oxazolyl]propionate

yield: 51%. colorless prism crystal, melting point: 97–98° C. (recrystallized from ethyl acetate-hexane).

Reference Example 119

methyl 3-[4-(4-chlorophenyl)-2-(2-naphthyl)-5-oxazolyl]propionate

yield: 47%. colorless prism crystal, melting point: 120–121° C. (recrystallized from ethyl acetate-hexane).

Reference Example 120

methyl 3-[4-(4-chlorophenyl)-2-(2-thienyl)-5-oxazolyl]propionate

yield: 37%. colorless prism crystal, melting point: 66–67° C. (recrystallized from hexane).

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Reference Example 121

methyl 3-[4-(4-chlorophenyl)-2-(4-methoxyphenyl)-5-oxazolyl]propionate

yield: 53%. colorless prism crystal, melting point: 83–84° C. (recrystallized from methanol).

Reference Example 122

methyl 3-[4-(4-chlorophenyl)-2-(1-propyl)-5-oxazolyl]propionate

yield: 62%. a yellow oil. NMR(CDCl₃) delta: 1.01 (3H, t, J=7.5 Hz), 1.75–1.85 (2H, m) 2.72 (2H, t, J=8 Hz), 2.73 (2H, t, J=7.5 Hz), 3.18 (2H, t, J=8 Hz), 3.68 (3H, s), 7.38 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.5 Hz).

Reference Example 123

A mixture of methyl 3-[4-(4-chlorophenyl)-2-[3,4-(methylenedioxy)phenyl]-5-oxazolyl]propionate (1.29 g), potassium hydroxide (0.44 g), methanol (20 mL) and tetrahydrofuran (15 mL) was stirred at room temperature for 2 hrs. The reaction mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated to give 3-[4-(4-chlorophenyl)-2-[3,4-(methylenedioxy)phenyl]-5-oxazolyl]propionic acid (1.22 g, 98%) as a colorless powder. Recrystallization from ethyl acetate-hexane gave colorless prism crystals. melting point: 199–200° C.

In the same manner as in Reference Example 123, the compounds of Reference Examples 124–143 were synthesized.

Reference Example 124

ethyl 3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-thiazolyl]propionate

yield: 88%. pale-yellow prism crystal, melting point: 81–82° C. (recrystallized from acetone-hexane).

Reference Example 125

3-[4-(3,4-dichlorophenyl)-2-phenyl-5-oxazolyl]propionic acid

yield: 98%. pale-yellow prism crystal, melting point: 197–198° C. (recrystallized from acetone-hexane).

Reference Example 126

6-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]hexanoic acid

yield: 79%. colorless prism crystal, melting point: 123–124° C. (recrystallized from ethanol-hexane).

Reference Example 127

3-[2-(1H-benzimidazol-1-yl)-4-(3,4-dichlorophenyl)-5-oxazolyl]propionic acid

yield: 91%. colorless prism crystal, melting point: 233–234° C. (recrystallized from acetone-hexane).

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Reference Example 128

3-[4-(4-chlorophenyl)-2-cyclohexyl-5-oxazolyl]propionic acid

yield: 98%. colorless prism crystal, melting point: 150–151° C. (recrystallized from ethyl acetate-hexane).

Reference Example 129

3-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]propionic acid

yield: 98%. colorless prism crystal, melting point: 175–176° C. (recrystallized from ethyl acetate).

Reference Example 130

3-[4-(4-chlorophenyl)-2-(4-fluorophenyl)-5-oxazolyl]propionic acid

yield: 93%. colorless prism crystal, melting point: 162–163° C. (recrystallized from ethyl acetate-hexane).

Example 131

3-[4-(4-chlorophenyl)-2-(2-naphthyl)-5-oxazolyl]propionic acid

yield: 97%. colorless prism crystal, melting point: 167–168° C. (recrystallized from ethyl acetate-hexane).

Reference Example 132

3-[4-(4-chlorophenyl)-2-(2-thienyl)-5-oxazolyl]propionic acid

yield: 94%. colorless prism crystal, melting point: 160–161° C. (recrystallized from ethyl acetate-hexane).

Reference Example 133

3-[4-(4-chlorophenyl)-2-(4-methoxyphenyl)-5-oxazolyl]propionic acid

yield: 93%. colorless prism crystal, melting point: 152–153° C. (recrystallized from ethanol).

Reference Example 134

3-[4-(4-chlorophenyl)-2-(1-propyl)-5-oxazole]propionic acid

yield: 84%. colorless prism crystal, melting point: 150–151° C. (recrystallized from ethanol).

Reference Example 135

3-[4-(4-chlorophenyl)-2-(1-naphthyl)-5-oxazolyl]propionic acid

yield: 89%. colorless prism crystal, melting point: 154–155° C. (recrystallized from isopropyl ether-hexane).

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Reference Example 136

3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-2-yl)-5-oxazolyl]propionic acid

yield: 91%, colorless prism crystal
melting point: 195–196° C. (recrystallized from ethyl acetate-hexane)

Reference Example 137

3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propionic acid

yield: 98%. colorless prism crystal melting point: 209–210° C. (recrystallized from isopropyl ether-hexane)

Reference Example 138

3-[4-(4-chlorophenyl)-2-(1H-indazol-3-yl)-5-oxazolyl]propionic acid

yield: 80%, colorless prism crystal melting point: 214–216° C. (recrystallized from isopropyl ether-hexane)

Reference Example 139

3-[4-(4-chlorophenyl)-2-(2,3-dichlorophenyl)-5-oxazolyl]propionic acid

yield: 90%. colorless prism crystal melting point: 166–167° C. (recrystallized from isopropyl ether-hexane)

Reference Example 140

2-(1H-benzoimidazol-1-yl)-4-(3-chlorophenyl)-5-oxazolepropionic acid

yield: 71%. pale-yellow solid NMR(CDCl₃) delta: 2.91 (2H, t, J=7.5 Hz), 3.37 (2H, t, J=7.5 Hz), 7.32–7.52 (4H, m), 7.60–7.64 (1H, m), 7.79 (1H, s), 7.87 (1H, d, J=8 Hz), 8.27 (1H, d, J=8.5 Hz), 8.62 (1H, s).

Reference Example 141

3-[2-(1H-benzoimidazol-1-yl)-4-phenyl-5-oxazolyl]propionic acid

yield: 91%. solid NMR(CDCl₃) delta: 2.89 (2H, t, J=7.5 Hz), 3.38 (2H, t, J=7.5 Hz), 7.34–7.56 (5H, m), 7.76 (2H, d, J=8 Hz), 7.86 (1H, d, J=7.5 Hz), 8.28 (1H, d, J=7.5 Hz), 8.64 (1H, s).

Reference Example 142

3-[2-(1H-benzoimidazol-1-yl)-4-(4-methoxyphenyl)-5-oxazolyl]propionic acid

yield: 81%, pale-yellow solid NMR(CDCl₃) delta: 2.88 (2H, t, J=7 Hz), 3.35 (2H, t, J=7 Hz), 3.87 (3H, s), 7.02 (2H, d, J=9 Hz), 7.34–7.52 (2H, m), 7.69 (2H, d, J=9 Hz), 7.86 (1H, d, J=8 Hz), 8.27 (1H, d, J=8 Hz), 8.62 (1H, s).

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Reference Example 143

3-[2-(1H-benzoimidazol-1-yl)-4-(4-fluorophenyl)-5-oxazolyl]propionic acid

yield: 70%. pale-yellow solid NMR(CDCl₃) delta: 2.89 (2H, t, J=7 Hz), 3.35 (2H, t, J=7 Hz), 7.10–7.24 (2H, m), 7.36–7.52 (2H, m), 7.68–7.80 (2H, m), 7.86 (1H, d, J=7 Hz), 8.26 (1H, d, J=7.5 Hz), 8.63 (1H, s).

Reference Example 144

A mixture of 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (1.0 g), 1-phenylpiperazine (2.27 g), potassium carbonate (2.42 g) and N,N-dimethylformamide (20 mL) was stirred at 100° C. for 3 hrs. The reaction mixture was poured into aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography and 3-[4-(4-chlorophenyl)-2-(4-phenyl-1-piperazinyl)-5-oxazolyl]propionic acid (0.76 g, yield 53%) was obtained as a powder from a fraction eluted with ethyl acetate-chloroform-methanol (10:10:1, volume ratio). Recrystallization from ethyl acetate gave colorless prism crystals. melting point: 177–178° C.

In the same manner as in Reference Example 144, the compounds of Reference Examples 145 and 146 were synthesized.

Reference Example 145

3-[4-(4-chlorophenyl)-2-(2-pyrimidinylsulfanyl)-5-oxazolyl]propionic acid

yield: 76%. colorless prism crystal, melting point: 198–199° C. (recrystallized from ethyl acetate).

Reference Example 146

3-[2-(N-benzylamino)-4-(4-chlorophenyl)-5-oxazolyl]propionic acid

yield: 86%. colorless prism crystal, melting point: 178–179° C. (recrystallized from ethyl acetate-hexane).

Reference Example 147

A mixture of 4-(4-chlorophenyl)-2-phenyloxazole (14.43 g), phosphorus oxychloride (12.97 g), N,N-dimethylformamide (100 mL) was stirred at 90° C. for 1.5 hrs. The reaction mixture was poured into iced water, and the precipitated solid was collected by filtration, washed successively with aqueous sodium hydrogen carbonate solution and water and dried. The obtained crystals were recrystallized from acetone-hexane to give 4-(4-chlorophenyl)-2-phenyl-5-oxazolecarbaldehyde (7.90 g, 49%) as yellow prism crystals. NMR(CDCl₃) delta: 7.45–7.65 (5H, m), 8.10 (2H, d, J=8.5 Hz), 8.2–8.25 (2H, m), 10.03 (1H, s).

A mixture of this compound (3.95 g), malonic acid (2.90 g), piperidine (0.36 g) and pyridine (80 mL) was stirred at 100° C. for 8 hrs. The reaction mixture was poured into iced water and acidified with 1N aqueous hydrochloric acid solution.

The mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate, and con-

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centrated to give (2E)-3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propionic acid (4.36 g, 96%) as a yellow powder. Recrystallization from ethyl acetate gave yellow prism crystals. melting point: 255–257° C.

Reference Example 148

Ethyl 5-(4-chlorophenyl)-5-oxopentanoate (30 g) was dissolved in diethyl ether (300 ml) and bromine (6.55 g) was added dropwise at room temperature. An aqueous sodium sulfite solution was added to the reaction mixture, and the mixture was neutralized with aqueous sodium hydrogen carbonate solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was dissolved in ethanol (200 mL) and thiourea (8.85 g) and sodium acetate (14.3 g) were added. The mixture was stirred with heating under reflux for 2 hrs. The reaction mixture was poured into water, and the precipitated solid was collected by filtration to give ethyl 3-[2-amino-4-(4-chlorophenyl)-1,3-thiazol-5-yl]propionate (30.2 g, 80%) as a colorless powder.

NMR(CDCl₃) delta: 1.24 (3H,t,J=7.5 Hz), 2.58 (2H,t,J=7 Hz), 3.08 (2H,t,J=7 Hz), 4.13 (2H,q,J=7.5 Hz), 4.97 (2H,s), 7.3–7.5 (4H,m).

This compound (30 g) was dissolved in a mixed solvent of tetrahydrofuran (300 ml)-ethanol (150 ml) and 2N aqueous sodium hydroxide solution was added at 0° C. The mixture was stirred at 60° C. for 1 hr. The reaction mixture was poured into water and 1N hydrochloric acid was added. The precipitated solid was collected by filtration to give 3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]propionic acid (25.9 g, 94%) as a yellow powder. Recrystallization from ethanol gave yellow prism crystals. melting point: 116–118° C.

Reference Example 149

4-(4-chlorophenyl)-5-[3-(1,1-dioxide-4-thiomorpholinyl)-3-oxopropyl]-1,3-thiazole-2-amine

In the same manner as in Reference Example 148, the title compound was produced.

yield: 22%. colorless prism crystal, melting point: 220–222° C. (recrystallized from ethanol-diisopropyl ether).

Example 1

A mixture of 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (0.50 g), oxalyl chloride (0.27 g), N,N-dimethylformamide (0.1 ml) and tetrahydrofuran (15 ml) was stirred at room temperature for 1 hr. The reaction mixture was concentrated and the residue was dissolved in tetrahydrofuran (15 ml). Thereto were added triethylamine (0.21 g) and diethyl 4-aminobenzylphosphonate (0.37 g) and the mixture was stirred at room temperature for 1.5 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate and then saturated brine, dried (MgSO₄) and concentrated to give a colorless powder (0.80 g). Recrystallization from ethanol gave 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide as colorless prism crystals (660 mg, 74%). melting point: 137–138° C.

In the same manner as in Example 1, the compounds of Examples 2–60 were synthesized.

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Example 2

3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide

yield: 22%. colorless prism crystals, melting point: 172–173° C. (recrystallized from ethanol).

Example 3

3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 10%. pale-yellow prism crystals, melting point: 158–159° C. (recrystallized from ethanol).

Example 4

3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide

yield: 33%. colorless prism crystals, melting point: 173–174° C. (recrystallized from ethanol).

Example 5

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 63%. colorless prism crystals, melting point: 159–160° C. (recrystallized from ethyl acetate-hexane).

Example 6

3-[4-(4-chlorophenyl)-2-(4-morpholinyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 76%. pale-yellow prism crystals, melting point: 186–187° C. (recrystallized from ethyl acetate-hexane).

Example 7

3-{4-(4-chlorophenyl)-2-[(4-methylphenyl)sulfanyl]-5-oxazolyl}-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 99%. a yellow oil. NMR(CDCl₃) delta: 1.23 (6H, t, J=7 Hz), 2.35 (3H,s), 2.71 (2H, t, J=8.5 Hz), 3.09 (2H, d, J=22 Hz), 3.22 (2H, d, J=8.5 Hz), 3.95–4.05 (4H, m), 7.16 (2H, d, J=8 Hz), 7.15–7.2 (2H, m), 7.35–7.4 (2H, m), 7.36 (2H, d, J=8.5 Hz), 7.46 (2H, d, J=8 Hz), 7.61 (2H, d, J=8.5 Hz), 8.00 (1H, s).

Example 8

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propionamide

yield: 47%. pale-yellow prism crystals, melting point: 265–266° C. (recrystallized from ethanol-chloroform).

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Example 9

3-[4-(4-chlorophenyl)-2-(4-morpholinyl)-5-oxazolyl]propionamide

yield: 70%. colorless prism crystal, melting point: 180–181° C. (recrystallized from ethyl acetate-hexane).

Example 10

3-[4-(4-chlorophenyl)-2-[(4-methylphenyl)sulfanyl]-5-oxazolyl]propionamide

yield: 50%. colorless prism crystals, melting point: 155–156° C. (recrystallized from ethyl acetate).

Example 11

N-(4-[[bis(ethylamide)phosphoryl]methyl]phenyl)-3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propionamide

yield: 44%. colorless prism crystals, melting point: 122–123° C. (recrystallized from ethyl acetate-hexane).

Example 12

3-[4-(4-chlorophenyl)-2-[3,4-(methylenedioxy)phenyl]-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 84%. colorless prism crystals, melting point: 155–156° C. (recrystallized from ethyl acetate-hexane).

Example 13

3-[4-(4-chlorophenyl)-2-cyclohexyl-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 76%. colorless prism crystals, melting point: 133–134° C. (recrystallized from ethyl acetate-hexane).

Example 14

3-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 76%. colorless prism crystals, melting point: 161–162° C. (recrystallized from ethyl acetate-hexane).

Example 15

3-[4-(4-chlorophenyl)-2-(4,5-dimethyl-1-imidazolyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 58%. colorless prism crystals, melting point: 179–180° C. (recrystallized from ethyl acetate-hexane).

Example 16

3-[4-(4-chlorophenyl)-2-[3,4-(methylenedioxy)phenyl]-5-oxazolyl]propionamide

yield: 84%. colorless prism crystals, melting point: 210–211° C. (recrystallized from ethyl acetate).

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Example 17

3-[4-(4-chlorophenyl)-2-cyclohexyl-5-oxazolyl]propionamide

yield: 70%. colorless prism crystals, melting point: 142–143° C. (recrystallized from ethyl acetate-hexane).

Example 18

3-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]propionamide

yield: 74%. colorless prism crystals, melting point: 169–170° C. (recrystallized from ethyl acetate-hexane).

Example 19

3-[4-(4-chlorophenyl)-2-(4,5-dimethyl-1-imidazolyl)-5-oxazolyl]propionamide

yield: 50%. colorless prism crystals, melting point: 232–233° C. (recrystallized from ethyl acetate-hexane).

Example 20

3-[4-(4-chlorophenyl)-2-(4-fluorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 19%. colorless prism crystals, melting point: 148–149° C. (recrystallized from ethyl acetate-hexane).

Example 21

3-[4-(4-chlorophenyl)-2-(2-naphthyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 76%. colorless prism crystals, melting point: 191–192° C. (recrystallized from ethanol).

Example 22

3-[4-(4-chlorophenyl)-2-(2-thienyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 77%. colorless prism crystals, melting point: 164–165° C. (recrystallized from ethyl acetate-hexane).

Example 23

3-[4-(4-chlorophenyl)-2-(4-fluorophenyl)-5-oxazolyl]propionamide

yield: 22%. colorless prism crystals, melting point: 212–213° C. (recrystallized from ethyl acetate).

Example 24

3-[4-(4-chlorophenyl)-2-(2-naphthyl)-5-oxazolyl]propionamide

yield: 84%. colorless prism crystals, melting point: 206–207° C. (recrystallized from ethyl acetate).

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Example 25

3-[4-(4-chlorophenyl)-2-(2-thienyl)-5-oxazolyl]propionamide

yield: 78%. colorless prism crystals, melting point: 226–227° C. (recrystallized from ethanol).

Example 26

3-[4-(4-chlorophenyl)-2-(4-methoxyphenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 85%. colorless prism crystals, melting point: 141–142° C. (recrystallized from ethyl acetate-hexane).

Example 27

3-[4-(4-chlorophenyl)-2-propyl-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 64%. colorless prism crystals, melting point: 108–109° C. (recrystallized from ethyl acetate-hexane).

Example 28

3-[4-(4-chlorophenyl)-2-(4-methoxyphenyl)-5-oxazolyl]propionamide

yield: 72%. colorless prism crystals, melting point: 215–216° C. (recrystallized from ethyl acetate).

Example 29

3-[4-(4-chlorophenyl)-2-propyl-5-oxazolyl]propionamide

yield: 74%. colorless prism crystals, melting point: 150–151° C. (recrystallized from ethyl acetate-hexane).

Example 30

3-[4-(4-chlorophenyl)-2-(4-phenyl-1-piperazinyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 70%. a yellow oil. NMR(CDCl₃) delta: 1.22 (6H, t, J=7 Hz), 2.72 (2H, t, J=7.5 Hz), 3.09 (2H, d, J=22 Hz), 3.2–3.3 (6H, m), 3.64 (4H, t, J=5 Hz), 3.95–4.05 (4H, m), 6.9–7.0 (3H, m), 7.2–7.45 (8H, m), 7.59 (2H, d, J=8.5 Hz), 7.91 (1H, s).

Example 31

3-[4-(4-chlorophenyl)-2-(4-phenyl-1-piperazinyl)-5-oxazolyl]propionamide

yield: 68%. colorless prism crystals, melting point: 187–188° C. (recrystallized from ethyl acetate).

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Example 32

3-[4-(4-chlorophenyl)-2-(2-pyrimidinylsulfanyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 70%. colorless prism crystals, melting point: 146–147° C. (recrystallized from ethyl acetate).

Example 33

3-[4-(4-chlorophenyl)-2-(2-pyrimidinylsulfanyl)-5-oxazolyl]propionamide

yield: 78%. colorless prism crystals, melting point: 194–195° C. (recrystallized from ethanol).

Example 34

3-[2-(benzylamino)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 21%. colorless prism crystals, melting point: 156–157° C. (recrystallized from ethyl acetate).

Example 35

3-[4-(4-chlorophenyl)-2-(2-pyridinylsulfanyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 72%. colorless prism crystals, melting point: 146–147° C. (recrystallized from ethyl acetate).

Example 36

3-[4-(4-chlorophenyl)-2-(2-pyridinylsulfanyl)-5-oxazolyl]propionamide

yield: 67%. colorless prism crystals, melting point: 162–163° C. (recrystallized from ethyl acetate).

Example 37

3-[4-(4-chlorophenyl)-2-phenoxy-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 76%. colorless prism crystals, melting point: 149–150° C. (recrystallized from ethyl acetate).

Example 38

3-[4-(4-chlorophenyl)-2-phenoxy-5-oxazolyl]propionamide

yield: 60%. colorless prism crystals, melting point: 139–140° C. (recrystallized from ethyl acetate).

Example 39

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-{4-[(5,5-dimethyl-2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide

yield: 62%. colorless prism crystals, melting point: 193–194° C. (recrystallized from ethyl acetate-hexane).

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Example 40

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-{4-
[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]
phenyl}propionamide

yield: 18%. colorless prism crystals, melting point:
224–225° C. (recrystallized from chloroform-ethanol).

Example 41

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-(3-
pyridinyl)propionamide

yield: 80%. colorless prism crystals, melting point:
204–205° C. (recrystallized from chloroform-ethanol).

Example 42

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-
(methoxycarbonyl)phenyl]propionamide

yield: 73%. colorless prism crystals, melting point:
198–200° C. (recrystallized from ethyl acetate-hexane).

Example 43

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propi-
onamide

yield: 79%. colorless prism crystals, melting point:
207–208° C. (recrystallized from ethanol-chloroform).

Example 44

3-[2-(1H-imidazol-1-yl)-4-(4-chlorophenyl)-5-ox-
azolyl]-N-(4-{[(methylamino)sulfonyl]
methyl}phenyl)propionamide

yield: 54%. colorless prism crystals, melting point:
224–225° C. (recrystallized from tetrahydrofuran-isopropyl
ether).

Example 45

3-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]-N-[4-
(methoxycarbonyl)phenyl]propionamide

yield: 91%. colorless prism crystals, melting point:
177–178° C. (recrystallized from ethyl acetate).

Example 46

3-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]propi-
onamide

yield: 71%. colorless prism crystals, melting point:
175–176° C. (recrystallized from ethyl acetate).

Example 47

4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-
(diethylphosphonomethyl)phenyl]butanamide

yield: 73%. colorless prism crystals, melting point:
152–153° C. (recrystallized from ethyl acetate-ethanol).

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Example 48

4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-{4-
[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]
phenyl}butanamide

yield: 50%. colorless prism crystals, melting point:
224–225° C. (recrystallized from ethanol-chloroform).

Example 49

N-ethyl-4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]
butanamide

yield: 78%. colorless prism crystals, melting point:
127–128° C. (recrystallized from ethyl acetate).

Example 50

4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-
(methoxycarbonyl)phenyl]butanamide

yield: 74%. colorless prism crystals, melting point:
170–171° C. (recrystallized from ethyl acetate).

Example 51

1-{4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]bu-
tanoyl}-4-phenylpiperazine

yield: 30%. colorless prism crystals, melting point:
104–105° C. (recrystallized from ethyl acetate-hexane).

Example 52

4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]butana-
mide

yield: 75%. colorless prism crystals, melting point:
168–169° C. (recrystallized from ethyl acetate).

Example 53

2-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-
(diethylphosphonomethyl)phenyl]acetamide

yield: 41%. colorless prism crystals, melting point:
173–174° C. (recrystallized from ethanol).

Example 54

(2E)-3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-
[4-(diethylphosphonomethyl)phenyl]propenamide

yield: 70%. pale-yellow prism crystals, melting point:
204–206° C. (recrystallized from ethanol).

Example 55

(2E)-3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]
propenamide

yield: 72%. colorless prism crystals, melting point:
240–241° C. (recrystallized from ethyl acetate-hexane).

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Example 56

(2E)-3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-(ethoxycarbonyl)phenyl]propenamide

yield: 98%. colorless prism crystals, melting point: 135–140° C. (recrystallized from ethyl acetate).

Example 57

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-(dimethylphosphonomethyl)phenyl]propionamide

yield: 74%. colorless prism crystals, melting point: 153–154° C. (recrystallized from ethanol-hexane).

Example 58

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide

yield: 77%. colorless prism crystals, melting point: 177–178° C. (recrystallized from ethanol-hexane).

Example 59

3-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 89%. colorless prism crystals, melting point: 164–165° C. (recrystallized from dichloromethane-isopropyl ether).

Example 60

3-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]-N-[4-(diethylphosphono)phenyl]propionamide

yield: 83%. colorless prism crystals, melting point: 186–187° C. (recrystallized from dichloromethane-isopropyl ether).

Example 61

To a mixture of 4-(4-chlorophenyl)-2-phenyl-5-oxazolepropionic acid (500 mg), triethylamine (230 mg) and tetrahydrofuran (10 ml) was added ethyl chlorocarbonate (250 mg) at –40° C., and the mixture was stirred for 1 hr. Diethyl 4-aminophenylphosphonate (420 mg) was added, and the mixture was stirred at room temperature for 5 hrs. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography and 3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-(diethylphosphono)phenyl]propionamide (295 mg, yield 36%) was obtained as colorless prism crystals from a fraction eluted with ethyl acetate-chloroform (1:1, volume ratio). melting point: 139–140° C. (recrystallized from dichloromethane-isopropyl ether).

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Example 62

In the same manner as in Example 61, 3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide was synthesized.

yield: 95%. colorless prism crystals, melting point: 143–144° C. (recrystallized from dichloromethane-isopropyl ether).

Example 63

A mixture of 3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-(ethoxycarbonyl)phenyl]propionamide (0.70 g), potassium hydroxide (0.26 g), ethanol (20 ml) and tetrahydrofuran (10 ml) was stirred at room temperature for 5 hrs and further stirred at 50° C. for 3 hrs. The reaction mixture was poured into water and acidified with 1N hydrochloric acid. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and then with saturated brine, dried over anhydrous magnesium sulfate, and concentrated to give a colorless powder. Recrystallization from chloroform-ethanol gave 4-({3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propanoyl}amino)benzoic acid as colorless prism crystals (0.51 g, 75%). melting point: 243–244° C.

In the same manner as in Example 63, the compounds of Examples 64 and 65 were synthesized.

Example 64

4-({3-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]propanoyl}amino)benzoic acid

yield: 95%. colorless prism crystals, melting point: 294–295° C. (recrystallized from ethanol-chloroform).

Example 65

4-({(2E)-3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propenoyl}amino)benzoic acid

yield: 40%. colorless prism crystals, melting point: 275–276° C. (recrystallized from ethyl acetate-hexane).

Example 66

A mixture of 4-({3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propanoyl}amino)benzoic acid (0.30 g), oxalyl chloride (0.10 g), N,N-dimethylformamide (0.1 ml) and tetrahydrofuran (10 ml) was stirred at room temperature for 1 hr. The reaction mixture was concentrated and the residue was dissolved in tetrahydrofuran (15 ml). Thereto was added 25% aqueous ammonia (3 ml) and the mixture was stirred at room temperature for 1.5 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and then with saturated brine, dried (MgSO₄), and concentrated to give a colorless powder (0.27 g). Recrystallization from chloroform-ethanol gave 4-({3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propanoyl}amino)benzamide as colorless prism crystals (0.15 g, 50%). melting point: 268–269° C.

In the same manner as in Example 66, the compounds of Examples 67 and 68 were synthesized.

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Example 67

4-({3-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]
propanoyl}amino)benzamide

yield: 55%. colorless prism crystals, melting point: 300°
C. or above (dec.) (recrystallized from tetrahydrofuran).

Example 68

4-({(2E)-3-[4-(4-chlorophenyl)-2-phenyl-5-ox-
azolyl]propenoyl}amino)benzamide

yield: 54%. colorless prism crystals, melting point:
274–275° C. (recrystallized from ethanol).

Example 69

A mixture of diethyl 4-aminobenzylphosphonate (0.73 g),
2-(1H-benzimidazol-1-yl)-4-[4-(trifluoromethyl)phenyl]-5-
oxazolepropionic acid (0.85 g), 1-hydroxy-1H-1,2,3-benzo-
triazole hydrate (0.46 g), 1-ethyl-3-(3-dimethylaminopro-
pyl)carbodiimide hydrochloride (0.56 g) and N,N-
dimethylformamide (20 ml) was stirred at room temperature
for 16 hrs. The reaction mixture was poured into water, and
the mixture was extracted with ethyl acetate. The ethyl
acetate layer was washed with dilute hydrochloric acid,
saturated aqueous sodium hydrogen carbonate, and then
with saturated brine, dried (MgSO₄) and concentrated. The
residue was subjected to silica gel column chromatography,
and 3-{2-(1H-benzimidazol-1-yl)-4-[4-(trifluoromethyl)
phenyl]-5-oxazolyl}-N-[(4-diethylphosphonomethyl)phe-
nyl]propionamide (0.70 g, yield 52%) was obtained as
colorless crystals from a fraction eluted with ethyl acetate-
hexane (2:1, volume ratio). Recrystallization from acetone-
isopropyl ether gave colorless prism crystals. melting point:
208–209° C.

In the same manner as in Example 69, the compounds of
Examples 70–223 were synthesized.

Example 70

3-[4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(dieth-
ylphosphonomethyl)phenyl]propionamide

yield: 92%. colorless prism crystals, melting point:
130–131° C. (recrystallized from ethyl acetate-hexane).

Example 71

3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-
oxazolyl]-N-(2-methoxyphenyl)propionamide

yield: 90%. colorless prism crystals, melting point:
153–154° C. (recrystallized from ethyl acetate-hexane).

Example 72

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-[3-(diethylphosphono)propyl]propiona-
mide

yield: 80%. colorless prism crystals, melting point:
130–131° C. (recrystallized from ethyl acetate).

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Example 73

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-[(4-dimethylphosphonomethyl)phenyl]
propionamide

yield: 65%. colorless prism crystals, melting point:
206–207° C. (recrystallized from ethanol-hexane).

Example 74

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-
yl)methyl]phenyl}propionamide

yield: 67%. colorless prism crystals, melting point:
240–241° C. (recrystallized from tetrahydrofuran-ethanol).

Example 75

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-{4-[(5,5-dimethyl-2-oxide-1,3,2-diox-
aphosphinan-2-yl)methyl]phenyl}propionamide

yield: 58%. colorless prism crystals, melting point:
206–207° C. (recrystallized from tetrahydrofuran-ethanol).

Example 76

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-[4-(ethoxycarbonylmethyl)phenyl]pro-
pionamide

yield: 53%. colorless prism crystals, melting point:
181–182° C. (recrystallized from tetrahydrofuran-ethanol).

Example 77

1-(4-chlorophenyl)-4-{4-[4-(4-chlorophenyl)-2-(2-
methyl-1-imidazolyl)-5-oxazolyl]
butanoyl}piperazine

yield: 67%. amorphous. NMR(CDCl₃) delta: 2.05–2.2
(2H, m), 2.43 (2H, t, J=7 Hz), 2.78 (3H, s), 3.0–3.1 (6H, m),
3.52 (2H, t, J=5 Hz), 3.75 (2H, t, J=5 Hz), 6.82 (2H, d, J=9
Hz), 7.00 (1H, d, J=2 Hz), 7.23 (2H, d, J=9 Hz), 7.41 (2H,
d, J=9 Hz), 7.47 (1H, d, J=2 Hz), 7.66 (2H, d, J=9 Hz).

Example 78

4-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]-N-[(4-
diethylphosphonomethyl)phenyl]butanamide

yield: 57%. amorphous. NMR(CDCl₃) delta: 1.25 (6H, t,
J=7 Hz), 2.1–2.2 (2H, m), 2.44 (2H, t, J=7.5 Hz), 2.98 (2H,
t, J=7 Hz), 3.11 (2H, d, J=21 Hz), 3.9–4.1 (4H, m), 7.15–7.25
(2H, m), 7.35 (2H, d, J=8.5 Hz), 7.35–7.5 (2H, m), 7.56 (2H,
d, J=8.5 Hz), 7.68 (1H, s).

Example 79

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-(4-chlorophenyl)propionamide

yield: 76%. colorless prism crystals, melting point:
248–249° C. (recrystallized from tetrahydrofuran-ethanol).

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Example 80

3-[4-(4-chlorophenyl)-2-(4,5-dimethyl-1H-benzimidazol-1-yl)-5-oxazolyl]-N-[(4-diethylphosphonomethyl)phenyl]propionamide

yield: 58%. colorless prism crystals, melting point: 198–199° C. (recrystallized from ethanol-hexane).

Example 81

3-[4-(4-chlorophenyl)-2-[4-(trifluoromethyl)phenyl]-N-[(4-dimethylphosphonomethyl)phenyl]propionamide

yield: 81%. colorless prism crystals, melting point: 138–139° C. (recrystallized from ethanol-hexane).

Example 82

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[(4-dimethylphosphonomethyl)phenyl]butanamide

yield: 72%. colorless prism crystals, melting point: 172–174° C. (recrystallized from ethanol-hexane).

Example 83

4-[4-(4-chlorophenyl)-2-(4,5-dimethyl-1H-benzimidazol-1-yl)-5-oxazolyl]-N-[(4-diethylphosphonomethyl)phenyl]butanamide

yield: 72%. colorless prism crystals, melting point: 172–174° C. (recrystallized from ethanol-hexane).

Example 84

4-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[(4-dimethylphosphonomethyl)phenyl]butanamide

yield: 54%. colorless prism crystals, melting point: 145–146° C. (recrystallized from ethanol-hexane).

Example 85

3-[2-(1H-benzimidazol-1-yl)-4-(3,4-dichlorophenyl)-5-oxazolyl]-N-[(4-diethylphosphonomethyl)phenyl]propionamide

yield: 59%. pale-yellow prism crystals, melting point: 175–176° C. (recrystallized from ethanol-hexane).

Example 86

3-[4-(3,4-dichlorophenyl)-2-phenyl-5-oxazolyl]-N-[(4-dimethylphosphonomethyl)phenyl]propionamide

yield: 85%. pale-yellow prism crystals, melting point: 162–163° C. (recrystallized from ethanol-hexane).

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Example 87

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-{[N-methyl-N-(4-tetrahydropyranyl)amino]methyl}phenyl)propionamide

yield: 60%. colorless prism crystals, melting point: 182–184° C. (recrystallized from tetrahydrofuran-ethyl acetate).

Example 88

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(1-piperidiny)methyl]phenyl}propionamide

yield: 73%. colorless prism crystals, melting point: 194–195° C. (recrystallized from acetone-isopropyl ether).

Example 89

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(cyanomethyl)phenyl]propionamide

yield: 73%. pale-yellow prism crystals, melting point: 212–214° C. (recrystallized from tetrahydrofuran-hexane).

Example 90

4-({3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}amino)phenylacetic acid

yield: 55%. pale-yellow prism crystals, melting point: 247–248° C. (recrystallized from tetrahydrofuran-hexane).

Example 91

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(methoxycarbonyl)phenyl]propionamide

yield: 70%. pale-yellow prism crystals, melting point: 249–250° C. (recrystallized from tetrahydrofuran-hexane).

Example 92

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(2-pyridinyl)ethyl]propionamide

yield: 70%. pale-yellow prism crystals, melting point: 150–151° C. (recrystallized from acetone-hexane).

Example 93

1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-(2-pyridinyl)piperazine

yield: 79%. pale-yellow prism crystals, melting point: 174–176° C. (recrystallized from ethyl acetate-hexane).

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Example 94

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-(4-{
[N-methyl-N-(4-tetrahydropyranyl)amino]
methyl}phenyl)propionamide

yield: 89%. colorless prism crystals, melting point:
154–155° C. (recrystallized from ethyl acetate-isopropyl
ether).

Example 95

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-{4-
[(1-piperidiny)methyl]phenyl}propionamide

yield: 70%. pale-yellow prism crystals, melting point:
223–225° C. (recrystallized from tetrahydrofuran-ethyl
acetate).

Example 96

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-{4-(methylsulfanyl)
phenyl}propionamide

yield: 47%. pale-yellow prism crystals, melting point:
276–277° C. (recrystallized from ethyl acetate-hexane).

Example 97

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-{4-(cyanomethyl)phenyl}butanamide

yield: 85%. NMR(CDCl₃) delta: 2.0–2.2 (2H,m),2.49
(2H, t, J=7.5 Hz), 3.12 (2H, d, J=7.5 Hz), 3.70 (2H, s), 7.23
(2H, d, J=8.5 Hz), 7.35–7.5 (6H, m), 7.70 (2H, d, J=8.5 Hz),
7.85–7.90 (1H, m), 8.02 (1H, s) 8.2–8.3 (1H, m), 8.57 (1H,
s).

Example 98

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-
yl)methyl]phenyl}butanamide

yield: 59%. pale-yellow prism crystals, melting point:
206–207° C. (recrystallized from tetrahydrofuran-isopropyl
ether).

Example 99

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-{4-[(5-methyl-2-oxide-1,3,2-dioxaphos-
phinan-2-yl)methyl]phenyl}butanamide

yield: 43%. pale-yellow prism crystals, melting point:
202–203° C. (recrystallized from).

Example 100

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-[3-(diethylphosphonomethyl)phenyl]
butanamide

yield: 68%. pale-yellow prism crystals, melting point:
135–136° C. (recrystallized from ethanol-hexane).

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Example 101

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-{4-[(4,6-dimethyl-2-oxide-1,3,2-diox-
aphosphinan-2-yl)methyl]phenyl}butanamide

yield: 89%. pale-yellow prism crystals, melting point:
149–150° C. (recrystallized from ethanol-hexane).

Example 102

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-[4-(diethylphosphonomethyl)-2-meth-
ylphenyl]butanamide

yield: 46%. pale-yellow prism crystals, melting point:
118–119° C. (recrystallized from ethanol-hexane).

Example 103

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-[4-(diethylphosphono)phenyl]butana-
mide

yield: 75%. pale-yellow prism crystals, melting point:
162–163° C. (recrystallized from ethanol-hexane).

Example 104

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-(4-[(2-thiazolyl)amino]
sulfonyl]phenyl)butanamide

yield: 79%. pale-yellow prism crystals, melting point:
243–244° C. (recrystallized from tetrahydrofuran-ethyl
acetate).

Example 105

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-[4-
(cyanomethyl)phenyl]propionamide

yield: 76%. pale-yellow prism crystals, melting point:
212–214° C. (recrystallized from ethyl acetate-hexane).

Example 106

2-[4-({3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophe-
nyl)-5-oxazolyl]propanoyl}amino)phenyl]-N,N-di-
ethylacetamide

yield: 72%. colorless prism crystals, melting point:
209–210° C. (recrystallized from tetrahydrofuran-isopropyl
ether).

Example 107

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-
oxazolyl]-N-[4-(diethylphosphono)phenyl]propiona-
mide

yield: 69%. pale-yellow prism crystals, melting point:
249–250° C. (recrystallized from ethyl acetate-hexane).

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Example 108

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[3-(hydroxymethyl)phenyl]propionamide

yield: 87%. pale-yellow prism crystals, melting point: 206–207° C. (recrystallized from ethanol-hexane).

Example 109

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(hydroxymethyl)phenyl]propionamide

yield: 93%. pale-yellow prism crystals, melting point: 159–160° C. (recrystallized from ethanol-hexane).

Example 110

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[3-(cyanomethyl)phenyl]propionamide

yield: 75%. colorless prism crystals, melting point: 188–189° C. (recrystallized from acetone-hexane).

Example 111

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(cyanomethyl)phenyl]propionamide

yield: 76%. pale-yellow prism crystals, melting point: 235–236° C. (recrystallized from acetone-hexane).

Example 112

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-cyanophenyl)propionamide

yield: 86%. pale-yellow prism crystals, melting point: 216–217° C. (recrystallized from ethyl acetate-hexane).

Example 113

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-cyanophenyl)propionamide

yield: 77%. pale-yellow prism crystals, melting point: 186–187° C. (recrystallized from ethyl acetate-hexane).

Example 114

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-methoxyphenyl)propionamide

yield: 77%. colorless prism crystals, melting point: 240–241° C. (recrystallized from ethanol-hexane).

Example 115

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-methoxyphenyl)propionamide

yield: 70%. colorless prism crystals, melting point: 194–195° C. (recrystallized from tetrahydrofuran-ethanol).

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Example 116

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-cyclohexylphenyl)propionamide

yield: 66%. colorless prism crystals, melting point: 216–217° C. (recrystallized from ethanol-hexane).

Example 117

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-tert-butylphenyl)propionamide

yield: 74%. colorless prism crystals, melting point: 219–220° C. (recrystallized from ethanol-hexane)

Example 118

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(4,6-dimethyl-2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide

yield: 48%. colorless prism crystals, melting point: 190–191° C. (recrystallized from ethanol-hexane).

Example 119

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(5-methyl-2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide

yield: 92%. pale-yellow prism crystals, melting point: 205–206° C. (recrystallized from ethanol-hexane).

Example 120

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-phenylpropionamide

yield: 78%. pale-yellow prism crystals, melting point: 226–227° C. (recrystallized from ethanol-hexane).

Example 121

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(trifluoromethyl)phenyl]propionamide

yield: 72%. colorless prism crystals, melting point: 259–263° C. (recrystallized from ethanol-hexane).

Example 122

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(trifluoromethoxy)phenyl]propionamide

yield: 66%. colorless prism crystals, melting point: 174–175° C. (recrystallized from ethanol-hexane)

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Example 123

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(dibutylphosphonomethyl)phenyl] butanamide

yield: 99%. a yellow oil. NMR(CDCl₃) delta: 0.89 (6H, t, J=7 Hz), 1.3–1.8 (8H,m), 2.2–2.4 (2H, m), 2.4–2.6 (2H, m), 3.0–3.2 (4H,m), 3.8–4.2 (4H, m), 7.1–7.3 (2H, m), 7.3–7.5 (7H, m), 7.71 (2H, d, J=8.5 Hz), 7.8–7.9 (1H,m), 8.2–8.3 (1H,m), 8.58 (1H, s).

Example 124

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(diethylphosphonomethyl)phenyl] butanamide

yield: 66%. pale-yellow prism crystals, melting point: 133–136° C. (recrystallized from ethanol-hexane).

Example 125

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-methylbenzyl)propionamide

yield: 53%. colorless prism crystals, melting point: 241–242° C. (recrystallized from ethanol-hexane).

Example 126

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-isopropylphenyl)propionamide

yield: 82%. colorless prism crystals, melting point: 232–233° C. (recrystallized from ethanol-hexane).

Example 127

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3,4,5-trimethoxyphenyl)propionamide

yield: 85%. colorless prism crystals, melting point: 228–229° C. (recrystallized from ethanol-hexane).

Example 128

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-fluorophenyl)propionamide

yield: 63%. colorless prism crystals, melting point: 221–222° C. (recrystallized from ethanol-hexane).

Example 129

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(methoxycarbonyl)methyl]-2-thiazolyl}propionamide

yield: 72%. pale-yellow prism crystals, melting point: 233–234° C. (recrystallized from acetone-isopropyl ether).

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Example 130

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(dimethylamino)phenyl]propionamide

yield: 61%. pale-yellow prism crystals, melting point: 212–214° C.

Example 131

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[2-(diethylphosphono)ethyl]phenyl}butanamide

yield: 72%. pale-yellow prism crystal, melting point: 116–117° C. (recrystallized from acetone-isopropyl ether).

Example 132

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-benzylpropionamide

yield: 76%. colorless prism crystals, melting point: 205–206° C. (recrystallized from tetrahydrofuran-ethanol).

Example 133

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-methoxybenzyl)propionamide

yield: 77%. colorless prism crystals, melting point: 210–211° C. (recrystallized from ethanol-hexane).

Example 134

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-chlorobenzyl)propionamide

yield: 56%. colorless prism crystals, melting point: 222–223° C. (recrystallized from ethanol-hexane).

Example 135

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(dimethylamino)benzyl]propionamide

yield: 60%. colorless prism crystals, melting point: 184–185° C. (recrystallized from ethanol-hexane).

Example 136

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-phenylethyl)propionamide

yield: 84%. colorless prism crystals, melting point: 164–165° C. (recrystallized from acetone-hexane).

Example 137

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-fluorobenzyl)propionamide

yield: 61%. colorless prism crystals, melting point: 202–203° C. (recrystallized from ethanol-hexane).

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Example 138

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(trifluoromethyl)benzyl]propionamide

yield: 55%. colorless prism crystals, melting point: 194–195° C. (recrystallized from ethanol-hexane).

Example 139

2-[4-(N-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}amino)phenyl]-N-(2-methoxyphenyl)acetamide

yield: 79%. colorless prism crystals, melting point: 258–259° C. (recrystallized from tetrahydrofuran-hexane).

Example 140

2-[4-(N-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}amino)phenyl]-N-[4-(dimethylamino)phenyl]acetamide

yield: 69%. colorless prism crystals, melting point: 169–170° C. (recrystallized from tetrahydrofuran-ethanol).

Example 141

3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]-N-[4-(cyanomethyl)phenyl]propionamide

yield: 74%. colorless prism crystals, melting point: 187–188° C. (recrystallized from acetone-hexane).

Example 142

2-[4-({3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}amino)phenyl]-N,N-dimethylacetamide

yield: 75%. colorless prism crystals, melting point: 207–208° C. (recrystallized from acetone-hexane).

Example 143

2-[4-({3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}amino)phenyl]-N-methylacetamide

yield: 61%. colorless prism crystals, melting point: 219–221° C. (recrystallized from acetone-hexane).

Example 144

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-tert-butylbenzyl]propionamide

yield: 75%. colorless prism crystals, melting point: 170–171° C. (recrystallized from acetone-hexane).

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Example 145

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-methoxybenzyl)propionamide

yield: 84%. colorless prism crystals, melting point: 210–212° C. (recrystallized from acetone-hexane).

Example 146

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-methylbenzyl)propionamide

yield: 86%. colorless prism crystals, melting point: 210–212° C. (recrystallized from tetrahydrofuran-hexane).

Example 147

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3,4-dichlorobenzyl)propionamide

yield: 63%. colorless prism crystals, melting point: 190–191° C. (recrystallized from acetone-hexane).

Example 148

2-({3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}amino)-N-benzylacetamide

yield: 78%. colorless prism crystals, melting point: 186–187° C. (recrystallized from acetone-hexane).

Example 149

2-({3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}amino)-N-phenylacetamide

yield: 67%. colorless prism crystals, melting point: 250–251° C. (recrystallized from tetrahydrofuran-hexane).

Example 150

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(1,2,3-thiadiazol-4-yl)benzyl]propionamide

yield: 74%. colorless prism crystals, melting point: 173–174° C. (recrystallized from acetone-hexane).

Example 151

N-[4-(aminosulfonyl)benzyl]-3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propionamide

yield: 77%. colorless prism crystals, melting point: 255–256° C. (recrystallized from tetrahydrofuran-hexane).

Example 152

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-chlorobenzyl)propionamide

yield: 80%. colorless prism crystals, melting point: 190–191° C. (recrystallized from acetone-hexane).

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Example 153

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-phenylbenzyl)propionamide

yield: 76%. colorless prism crystals, melting point: 214–216° C. (recrystallized from tetrahydrofuran-hexane).

Example 154

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-pyridinylmethyl)propionamide

yield: 68%. colorless prism crystals, melting point: 157–158° C. (recrystallized from acetone-hexane).

Example 155

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-pyridinylmethyl)propionamide

yield: 70%. colorless prism crystals, melting point: 214–216° C. (recrystallized from acetone-hexane).

Example 156

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,6-difluorobenzyl)propionamide

yield: 97%. colorless prism crystals, melting point: 225–226° C. (recrystallized from acetone-hexane).

Example 157

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(trifluoromethyl)benzyl]propionamide

yield: 97%. colorless prism crystals, melting point: 208–209° C. (recrystallized from acetone-hexane).

Example 158

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,5-difluorobenzyl)propionamide

yield: 90%. colorless prism crystals, melting point: 197–198° C. (recrystallized from acetone-hexane).

Example 159

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-chloro-2-fluorobenzyl)propionamide

yield: 94%. colorless prism crystals, melting point: 189–191° C. (recrystallized from acetone-hexane).

Example 160

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,4-difluorobenzyl)propionamide

yield: 98%. colorless prism crystals, melting point: 190–191° C. (recrystallized from acetone-hexane).

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Example 161

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,4,6-trimethoxybenzyl)propionamide

yield: 95%. colorless prism crystals, melting point: 206–208° C. (recrystallized from acetone-hexane).

Example 162

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-phenoxyethyl)propionamide

yield: 95%. colorless prism crystals, melting point: 156–157° C. (recrystallized from acetone-hexane).

Example 163

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[3-fluoro-5-(trifluoromethyl)benzyl]propionamide

yield: 90%. colorless prism crystals, melting point: 198–200° C. (recrystallized from acetone-hexane).

Example 164

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3,5-difluorobenzyl)propionamide

yield: 70%. colorless prism crystals, melting point: 155–156° C. (recrystallized from acetone-hexane).

Example 165

N-[4-(aminosulfonyl)benzyl]-3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]propionamide

yield: 92%. colorless prism crystals, melting point: 225–227° C. (recrystallized from acetone-hexane).

Example 166

3-[4-(4-chlorophenyl)-2-phenyl-5-oxazolyl]-N-(4-methylbenzyl)propionamide

yield: 98%. colorless prism crystals, melting point: 193–194° C. (recrystallized from acetone-hexane).

Example 167

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(5-bromo-2-fluorobenzyl)propionamide

yield: 96%. colorless prism crystals, melting point: 183–184° C. (recrystallized from acetone-hexane).

Example 168

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2-chloro-4-fluorobenzyl)propionamide

yield: 92%. colorless prism crystals, melting point: 196–198° C. (recrystallized from acetone-hexane).

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Example 169

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3,4,5-trimethoxybenzyl)propionamide

yield: 87%. colorless prism crystals, melting point: 169–170° C. (recrystallized from acetone-hexane).

Example 170

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3-bromo-4-fluorobenzyl)propionamide

yield: 75%. colorless needle crystals, melting point: 206–207° C. (recrystallized from acetone-hexane).

Example 171

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3-bromobenzyl)propionamide

yield: 95%. colorless prism crystals, melting point: 181–183° C. (recrystallized from acetone-hexane).

Example 172

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-bromobenzyl)propionamide

yield: 84%. colorless prism crystals, melting point: 205–206° C. (recrystallized from acetone-hexane).

Example 173

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3-chloro-4-fluorobenzyl)propionamide

yield: 83%. colorless prism crystals, melting point: 188–189° C. (recrystallized from acetone-hexane).

Example 174

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,5-dichlorobenzyl)propionamide

yield: 78%. colorless prism crystals, melting point: 205–207° C. (recrystallized from acetone-hexane).

Example 175

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,4-dimethylbenzyl)propionamide

yield: 76%. colorless prism crystals, melting point: 218–219° C. (recrystallized from acetone-hexane).

Example 176

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(5-chloro-2-methylbenzyl)propionamide

yield: 80%. colorless prism crystals, melting point: 217–219° C. (recrystallized from acetone-hexane).

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Example 177

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3-phenylbenzyl)propionamide

yield: 70%. colorless prism crystals, melting point: 201–202° C. (recrystallized from acetone-hexane).

Example 178

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-chloro-2-methylbenzyl)propionamide

yield: 80%. colorless prism crystals, melting point: 200–201° C. (recrystallized from acetone-hexane).

Example 179

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,5-dimethoxybenzyl)propionamide

yield: 68%. colorless prism crystals, melting point: 193–194° C. (recrystallized from acetone-hexane).

Example 180

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(3,5-dimethoxybenzyl)propionamide

yield: 40%. colorless prism crystals, melting point: 198–200° C. (recrystallized from acetone-hexane).

Example 181

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(2,5-dimethylbenzyl)propionamide

yield: 76%. colorless prism crystals, melting point: 218–219° C. (recrystallized from acetone-hexane).

Example 182

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylpropionamide

yield: 71%. amorphous.
elemental analysis: for C₃₀H₂₉ClN₄O₄ Calculated C, 66.11; H, 5.36; N, 10.28. Found C, 66.06; H, 5.28; N, 10.12.

Example 183

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-benzyl-N-methylpropionamide

yield: 75%. amorphous.
elemental analysis: for C₂₇H₂₃ClN₄O₂ Calculated C, 68.86; H, 4.92; N, 11.90. Found C, 68.77; H, 4.89; N, 11.87.

Example 184

1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-2-(ethoxycarbonyl)piperidine

yield: 96%. amorphous.
elemental analysis: for C₂₇H₂₇ClN₄O₄ Calculated C, 63.96; H, 5.37; N, 11.05. Found C, 63.77; H, 5.33; N, 10.99.

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Example 185

1-{3-[2-(1H-benzimidazol-1-yl)-3-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}piperazine hydrochloride

yield: 52%. colorless prism crystals, melting point: 240–243° C. (recrystallized from ethanol-isopropyl ether).

Example 186

3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-oxazolyl]-N-[2-(4-morpholinyl)ethyl]propionamide

yield: 61%. a yellow oil. NMR(CDCl₃) delta: 2.3–2.5 (6H,m), 2.74 (2H, t, J=7.5 Hz), 3.3–3.4 (4H,m), 3.55–3.65 (4H,m), 7.4–7.5 (4H, m), 7.75 (2H, d, J=8.5 Hz), 7.85–7.9 (1H, m), 8.2–8.25 (1H, m), 8.57 (1H, s).

Example 187

3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-oxazolyl]-N-[3-(4-morpholinyl)propyl]propionamide

yield: 66%. a yellow oil. NMR(CDCl₃) delta: 1.5–1.7 (2H,m), 2.3–2.45 (6H,m), 2.63 (2H, t, J=7.5 Hz), 3.3–3.4 (4H,m), 3.55–3.65 (4H,m), 7.06 (1H, s), 7.4–7.55 (4H, m), 7.75 (2H, d, J=8.5 Hz), 7.85–7.9 (1H, m), 8.2–8.25 (1H, m), 8.57 (1H, s).

Example 188

3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-oxazolyl]-N-[2-(1-piperidinyl)ethyl]propionamide

yield: 55%. a yellow oil. NMR(CDCl₃) delta: 1.3–1.6 (4H,m), 2.25–2.45 (6H,m), 2.70 (2H, t, J=7.5 Hz), 3.3–3.4 (6H,m), 6.31 (1H, s), 7.4–7.55 (4H, m), 7.74 (2H, d, J=8.5 Hz), 7.85–7.9 (1H, m), 8.2–8.25 (1H, m), 8.58 (1H, s).

Example 189

3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-oxazolyl]-N-[2-(1-pyrrolidinyl)ethyl]propionamide

yield: 79%. a yellow oil. NMR(CDCl₃) delta: 1.9–2.1 (4H,m), 2.82 (2H, t, J=7.5 Hz), 2.9–3.1 (6H,m), 3.37 (2H, d, J=7.5 Hz), 3.5–3.6 (2H,m), 7.4–7.55 (4H, m), 7.76 (2H, d, J=8.5 Hz), 7.85–7.9 (1H, m), 8.25–8.3 (1H, m), 8.63 (1H, s).

Example 190

3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-oxazolyl]-N-[3-(1-imidazolyl)propyl]propionamide

yield: 59%. a yellow oil. NMR(CDCl₃) delta: 1.95–2.1 (2H,m), 2.65 (2H, t, J=7.5 Hz), 3.2–3.4 (4H,m), 3.9–4.0 (2H,m), 6.88 (1H,s), 7.11 (1H, s), 7.35–7.5 (4H,m), 7.74 (2H, d, J=8.5 Hz), 7.85–7.9 (1H, m), 8.2–8.25 (1H, m), 8.51 (1H, s).

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Example 191

(3S)-1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-3-(trifluoroacetamide)pyrrolidine

yield: 82%. colorless prism crystals, melting point: 190–191° C. (recrystallized from acetone-hexane).

Example 192

1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 85%. colorless prism crystals, melting point: 182–183° C. (recrystallized from acetone-hexane).

Example 193

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-methyl-N-(1-methyl-4-piperidinyl)propionamide

yield: 75%. colorless prism crystals, melting point: 133–134° C. (recrystallized from acetone-hexane).

Example 194

4-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 83%. colorless prism crystals, melting point: 227–228° C. (recrystallized from acetone-hexane).

Example 195

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(5-bromo-2-fluorobenzyl)butanamide

yield: 62%. colorless prism crystals, melting point: 196–198° C. (recrystallized from acetone-hexane).

Example 196

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-methylbenzyl)butanamide

yield: 60%. colorless prism crystals, melting point: 190–191° C. (recrystallized from acetone-hexane).

Example 197

4-[4-(4-chlorophenyl)-2-(1-pyrrolidinyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]butanamide

yield: 25%. pale-yellow prism crystals, melting point: 127–128° C. (recrystallized from acetone-hexane).

Example 198

4-{4-(4-chlorophenyl)-2-[4-(2-pyridinyl)-1-piperazinyl]-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]butanamide

yield: 11%. pale-yellow prism crystals, melting point: 114–116° C. (recrystallized from acetone-hexane).

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Example 199

4-{4-(4-chlorophenyl)-2-[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-piperazinyl]-5-oxazolyl}-N-[4-(diethylphosphonomethyl)phenyl]butanamide

yield: 11%. pale-yellow prism crystals, melting point: 205–209° C. (recrystallized from acetone-hexane).

Example 200

4-[4-(4-chlorophenyl)-2-(N-benzyl-N-methylamino)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]butanamide

yield: 39%. a yellow oil. NMR(CDCl₃) delta: 1.24 (6H, t, J=7 Hz), 2.05–2.15 (2H, m), 2.34 (2H, t, J=7 Hz), 2.88 (2H, t, J=7 Hz), 3.02 (3H, s), 3.11 (2H, d, J=22 Hz), 3.95–4.05 (4H, m), 4.61 (2H, s), 7.15–7.4 (12H, m), 7.57 (2H, d, J=8.5 Hz).

Example 201

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 62%. colorless prism crystals, melting point: 150–151° C. (recrystallized from acetone-hexane).

Example 202

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-(5-bromo-2-fluorobenzyl)propionamide

yield: 70%. colorless prism crystals, melting point: 188–189° C. (recrystallized from acetone-hexane).

Example 203

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-(4-methylbenzyl)propionamide

yield: 70%. colorless prism crystals, melting point: 191–192° C. (recrystallized from tetrahydrofuran-hexane).

Example 204

3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 64%. colorless prism crystals, melting point: 142–143° C. (recrystallized from acetone-hexane).

Example 205

1-{3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-thiazolyl]propanoyl}-4-piperidinol

yield: 92%. pale-yellow solid, HPLC analysis: purity 99.8% (retention time: 3.348 min.) MS (ESI+): 433 (M+H)

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Example 206

1-{3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-thiazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 92%. pale-yellow solid, HPLC analysis: purity 99.7% (retention time: 3.570 min.) MS (ESI+): 467 (M+H)

Example 207

1-{3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-thiazolyl]propanoyl}thiomorpholine-1-oxide

pale-yellow solid, HPLC analysis: purity 88.9% (retention time: 3.245 min.) MS (ESI+): 451 (M+H)

Example 208

(3S)-1-{3-[4-(4-chlorophenyl)-2-(1H-benzimidazol-1-yl)-5-thiazolyl]propanoyl}-3-(trifluoroacetamide)pyrrolidine

yield: 92%. pale-yellow solid, HPLC analysis: purity 98.3% (retention time: 3.778 min.) MS (ESI+) : 514 (M+H)

Example 209

(2E)-3-[2-(1H-benzimidazol-1-yl)-4-methyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 68%. colorless prism crystals, melting point: 150–151° C. (recrystallized from acetone-hexane).

Example 210

(2E)-3-[2-(1H-benzimidazol-1-yl)-4-tert-butyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 67%. colorless prism crystals, melting point: 211–212° C. (recrystallized from acetone-hexane).

Example 211

(2E)-3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 49%. colorless prism crystals, melting point: 198–199° C. (recrystallized from acetone-hexane).

Example 212

(2E)-3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 37%. yellow prism crystals, melting point: 229–230° C. (recrystallized from acetone-hexane).

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Example 213

3-[2-(1H-benzimidazol-1-yl)-4-tert-butyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 70%. colorless prism crystals, melting point: 155–156° C. (recrystallized from acetone-hexane).

Example 214

3-[2-(1H-benzimidazol-1-yl)-4-isopropyl-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 71%. yellow prism crystals, melting point: 171–172° C. (recrystallized from acetone-hexane).

Example 215

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]butanamide

yield: 75%. colorless prism crystals, melting point: 140–141° C. (recrystallized from acetone-hexane).

Example 216

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-(5-bromo-2-fluorobenzyl)butanamide

yield: 82%. colorless prism crystals, melting point: 160–161° C. (recrystallized from acetone-hexane).

Example 217

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-(4-methylbenzyl)butanamide

yield: 73%. colorless prism crystals, melting point: 138–139° C. (recrystallized from acetone-hexane).

Example 218

2-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]acetamide

yield: 87%. colorless prism crystals, melting point: 154–155° C. (recrystallized from acetone-isopropyl ether).

Example 219

2-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(cyanomethyl)phenyl]acetamide

yield: 75%. colorless prism crystals, melting point: 245–246° C. (recrystallized from tetrahydrofuran-isopropyl ether).

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Example 220

6-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]hexanamide

yield: 70%. colorless prism crystals, melting point: 149–151° C. (recrystallized from ethanol-hexane).

Example 221

6-[4-(4-chlorophenyl)-2-phenyl-5-thiazolyl]-N-[4-(dimethylphosphonomethyl)phenyl]hexanamide

yield: 81%. colorless prism crystals, melting point: 164–165° C. (recrystallized from ethanol-hexane).

Example 222

5-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]pentanamide

yield: 67%. colorless prism crystals, melting point: 168–169° C. (recrystallized from ethanol-hexane).

Example 223

5-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(cyanomethyl)phenyl]pentanamide

yield: 68%. colorless prism crystals, melting point: 187–188° C. (recrystallized from ethanol-hexane).

Example 224

A mixture of 3-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide (0.40 g), imidazole (0.20 g), potassium carbonate (0.41 g) and N,N-dimethylformamide (5 ml) was stirred at 120° C. for 2 hrs. The reaction mixture was poured into water, and the precipitated crystals were collected by filtration through a glass filter. The obtained crystals were washed with water and dried by ventilation. Recrystallization from acetone-isopropyl ether gave 3-[4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide as pale-yellow prism crystals (0.33 g, 78%), melting point: 196–197° C.

In the same manner as in Example 224, the compounds of Examples 225 and 226 were synthesized.

Example 225

3-[2-(1H-1,2,3-benzotriazole-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 33%. pale-yellow prism crystals, melting point: 91–92° C. (recrystallized from acetone-isopropyl ether).

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Example 226

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[(4-diethylphosphonomethyl)phenyl]butanamide

yield: 19%. pale-yellow prism crystals, melting point: 177–179° C. (recrystallized from acetone-isopropyl ether).

Example 227A

To a solution of 2-amino-4-(4-chlorophenyl)-5-thiazolepropionic acid (8.35 g), diethyl cyanophosphate (5.78 g) and diethyl 4-aminobenzylphosphonate (7.18 g) in N,N-dimethylformamide (100 ml) was added triethylamine (3.0 g) at 0° C. and the mixture was stirred at room temperature for 16 hrs.

The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated to give 3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide as crystals (8.28 g, 55%). Recrystallization from ethyl acetate-ethanol gave colorless prism crystals. melting point: 177–178° C.

Example 227B

A mixture of 3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]propionic acid (2.67 g), diethyl cyanophosphate (1.69 g), thiomorpholine-1,1-dioxide hydrochloride (1.62 g), triethylamine (2.9 ml) and N,N-dimethylformamide (40 ml) was stirred at room temperature for 3 hrs. The reaction mixture as poured into water, extracted with ethyl acetate, washed with 0.1N aqueous sodium hydroxide solution and water, dried over anhydrous magnesium sulfate and concentrated. The precipitated solid was collected by filtration to give 4-{3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]propanoyl}thiomorpholine-1,1-dioxide as a colorless powder. Recrystallization from ethanol-isopropyl ether gave colorless prism crystals. melting point: 220–222° C.

Example 228

A mixture of 3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide (500 mg), N,N-dimethylformamidedimethylacetal (155 mg) and N,N-dimethylformamide (10 ml) was stirred at room temperature for 1 hr. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography and 3-(4-(4-chlorophenyl)-2-{(E)-[(dimethylamino)methylidene]amino}-5-thiazolyl)-N-[4-(diethylphosphonomethyl)phenyl]propionamide was obtained as crystals (510 mg, yield: 92%) from a fraction eluted with 5% methanol-ethyl acetate. Recrystallization from ethyl acetate gave colorless prism crystals. melting point: 150–151° C.

Example 229

A mixture of 3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide (500 mg), pyridine-2-carboxylic acid (145 mg), 1-hydroxybenzotriazole (180 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (225 mg) and N,N-dimethylforma-

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5 midate (10 ml) was stirred at room temperature for 24 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated to give 3-{4-(4-chlorophenyl)-2-[(2-pyridinylcarbonyl)amino]-5-thiazolyl}-N-[4-(diethylphosphonomethyl)phenyl]propionamide was obtained as crystals (560 mg). Recrystallization from ethyl acetate gave colorless prism crystals (350 mg, yield: 58%). melting point: 184–185° C.

Example 230

15 A mixture of 3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide (400 mg), tert-butyl isocyanate (780 mg) and toluene (10 ml) was stirred at 70–80° C. for 20 hrs. The reaction mixture was concentrated. The residue was purified by silica gel column chromatography and 3-(4-(4-chlorophenyl)-2-[(tert-butylamino)carbonyl]amino)-5-thiazolyl)-N-[4-(diethylphosphonomethyl)phenyl]propionamide was obtained as crystals (395 mg, yield: 83%) from a fraction eluted with 3% methanol-ethyl acetate. Recrystallization from ethyl acetate gave colorless prism crystals. melting point: 180–181° C.

25 In the same manner as in Examples 229 and 230, a reaction of 3-[2-amino-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide with carboxylic acid or isocyanate (thio isocyanate) was carried out to synthesize the compounds of Examples 231–239.

Example 231

3-(4-(4-chlorophenyl)-2-[(methylamino)carbonyl]amino)-5-thiazolyl)-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 61%. colorless prism crystals, melting point: 206–207° C. (recrystallized from ethyl acetate).

Example 232

3-[4-(4-chlorophenyl)-2-[(dimethylamino)methyl]carbonyl]amino)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 54%. amorphous. elemental analysis: for C₂₇H₃₄ClN₄O₅PS.0.5H₂O Calculated C, 53.86; H, 5.86; N, 9.31. Found C, 53.97; H, 5.73; N, 9.41.

Example 233

3-(4-(4-chlorophenyl)-2-[(benzylamino)carbonyl]amino)-5-thiazolyl)-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 97%. colorless needle crystals, melting point: 144–145° C. (recrystallized from methanol-ethyl acetate).

Example 234

3-(4-(4-chlorophenyl)-2-[(phenylamino)carbonyl]amino)-5-thiazolyl)-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 91%. colorless prism crystals, melting point: 175–176° C. (recrystallized from methanol-ethyl acetate).

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Example 235

3-{4-(4-chlorophenyl)-2-[(phenylsulfonyl)amino]-5-thiazolyl}-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 91%. colorless needle crystals, melting point: 213–214° C. (recrystallized from methanol-ethyl acetate).

Example 236

3-[2-(benzoylamino)-4-(4-chlorophenyl)-5-thiazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 91%. colorless prism crystals, melting point: 171–172° C. (recrystallized from ethyl acetate-isopropyl ether).

Example 237

3-(4-(4-chlorophenyl)-2-[(benzylamino)thiocarbonylamino]-5-thiazolyl)-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 39%. colorless prism crystals, melting point: 202–203° C. (recrystallized from methanol-ethyl acetate).

Example 238

3-(4-(4-chlorophenyl)-2-[(benzoylamino)thiocarbonylamino]-5-thiazolyl)-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 72%. pale-yellow prism crystals, melting point: 208–209° C. (recrystallized from acetone-isopropyl ether).

Example 239

3-{4-(4-chlorophenyl)-2-[(3-phenylpropanoyl)amino]-5-thiazolyl}-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 72%. pale-yellow prism crystals, melting point: 208–209° C. (recrystallized from acetone-isopropyl ether).

Example 240

A mixture of 3-[4-(4-chlorophenyl)-2-methyl-5-oxazolyl]propionic acid (50 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (37 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (42 mg) and N,N-dimethylformamide (0.5 ml) was stirred overnight at room temperature. To the reaction mixture was added 0.1N aqueous hydrochloric acid solution (2 ml) and the reaction mixture was extracted with ethyl acetate (5 ml). The organic layer was concentrated and purified by Mega Bond Elut SCX (manufactured by Varian Inc.) (developing solvent: developed with ethyl acetate and then with 2M ammonia methanol solution) to give 3-[4-(4-chlorophenyl)-2-methyl-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide (78.0 mg, yield 79%). Recrystallization from ethyl acetate-hexane gave colorless prism crystals, melting point: 155–156° C. MS (ESI+): 491 (M+H)

In the same manner as in Example 240, the compounds of Examples 241–258 were synthesized.

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Example 241

4-{3-[4-(4-chlorophenyl)-2-methyl-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 65%. colorless prism crystals, melting point: 124–125° C. (recrystallized from ethyl acetate-hexane). MS (ESI+): 383 (M+H)

Example 242

1-{3-[4-(4-chlorophenyl)-2-methyl-5-oxazolyl]propanoyl}-4-piperidinol

yield: 74% HPLC analysis: purity 96.0% (retention time: 3.243 min.) MS (ESI+): 349 (M+H)

Example 243

3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 60%. yellow prism crystals, melting point: 148–149° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 95.3% (retention time: 4.045 min.) MS (ESI+): 559 (M+H)

Example 244

3-[2-(1H-benzimidazol-1-yl)-4-(4-methoxyphenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 31%. yellow prism crystals, melting point: 143–144° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 97.5% (retention time: 4.025 min.) MS (ESI+): 589 (M+H)

Example 245

4-{3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 28%. colorless prism crystals, melting point: 177–179° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 98.5% (retention time: 3.727 min.) MS (ESI+): 451 (M+H)

Example 246

4-{3-[2-(1H-benzimidazol-1-yl)-4-(4-methoxyphenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 44%. yellow prism crystals, melting point: 214–215° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 98.0% (retention time: 3.725 min.) MS (ESI+): 481 (M+H)

Example 247

1-{3-[2-(1H-benzimidazol-1-yl)-4-phenyl-5-oxazolyl]propanoyl}-4-piperidinol

yield: 61%. colorless prism crystals, melting point: 157–158° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 96.8% (retention time: 3.588 min.) MS (ESI+): 417 (M+H)

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Example 248

1-(3-[2-(1H-benzoimidazol-1-yl)-4-(4-methoxyphenyl)-5-oxazolyl]propanoyl)-4-piperidinol

5

yield: 46%. yellow prism crystals, melting point: 161–162° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 97.7% (retention time: 3.581 min.) MS (ESI+): 447 (M+H)

10

Example 249

1-{3-[2-(1H-benzoimidazol-1-yl)-4-phenyl-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine

15

yield: 11% HPLC analysis: purity 99.0% (retention time: 2.981 min.) MS (ESI+): 513 (M+H)

20

Example 250

1-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-methoxyphenyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine

25

yield: 17%. yellow prism crystals, melting point: dec. at 170° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 94.3% (retention time: 2.979 min.) MS (ESI+) : 543 (M+H)

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Example 251

1-{3-[2-(1H-benzoimidazol-1-yl)-4-phenyl-5-oxazolyl]propanoyl}-4-[(1-methylpiperidin-3-yl)methyl]piperazine

35

yield: 24% HPLC analysis: purity 95.3% (retention time: 2.976 min.) MS (ESI+): 513 (M+H)

40

Example 252

1-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-methoxyphenyl)-5-oxazolyl]propanoyl}-4-[(1-methylpiperidin-3-yl)methyl]piperazine

45

yield: 26%. yellow prism crystals, melting point: 151–152° C. (recrystallized from ethyl acetate-hexane). HPLC analysis: purity 96.6% (retention time: 2.981 min.) MS (ESI+): 543 (M+H)

50

Example 253

3-[2-(1H-benzoimidazol-1-yl)-4-(3-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

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yield: 64%. yellow prism crystals, melting point: 98–99° C. (recrystallized from ethyl acetate-hexane). MS (ESI+): 593 (M+H)

65

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Example 254

3-[2-(1H-benzoimidazol-1-yl)-4-(4-fluorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 61%. yellow prism crystals, melting point: 95–96° C. (recrystallized from ethyl acetate-hexane). MS (ESI+): 577 (M+H)

Example 255

4-{3-[2-(1H-benzoimidazol-1-yl)-4-(3-chlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 53%. colorless prism crystals, melting point: 186–187° C. (recrystallized from ethyl acetate-hexane). MS (ESI+): 485 (M+H)

Example 256

4-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-fluorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 59%. colorless prism crystals, melting point: 224–225° C. (recrystallized from ethyl acetate-hexane). MS (ESI+): 469 (M+H)

Example 257

1-{3-[2-(1H-benzoimidazol-1-yl)-4-(3-chlorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 63%. colorless prism crystals, melting point: 97–98° C. (recrystallized from ethyl acetate-hexane). MS (ESI+): 451 (M+H)

Example 258

1-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-fluorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 58%. yellow prism crystals, melting point: 158–159° C. (recrystallized from ethyl acetate-hexane). MS (ESI+): 435 (M+H)

Example 259

A mixture of thiazolidine (145 mg), 3-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (300 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (222 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (253 mg) and N,N-dimethylformamide (1 ml) was stirred overnight at room temperature. To the reaction mixture was added 0.1N aqueous hydrochloric acid solution (16 ml) and the reaction mixture was extracted with ethyl acetate (5 ml). The organic layer was concentrated, introduced into preparative HPLC and purified to give 3-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiazolidine (165 mg, 46%). Recrystallization from ethyl acetate-hexane gave yellow prism crystals, melting point: 125–126° C.

HPLC analysis: purity 100% (retention time: 4.291 min.) MS (ESI+) : 439 (M+H)

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In the same manner as in Example 259, the compounds of Examples 260–296 were synthesized.

Example 260

1-[(1-methyl-4-piperidinyl)methyl]-4-[3-(4-phenyl-5-oxazolyl)propanoyl]piperazine bis trifluoroacetate

yield: 29% HPLC analysis: purity 93.1% (retention time: 2.168 min.) MS (ESI+): 397 (M+H)

Example 261

1-[(1-methyl-4-piperidinyl)methyl]-4-(3-{4-phenyl-2-(E)-2-phenylethenyl}-5-oxazolyl)propanoyl)piperazine bis trifluoroacetate

yield: 46% HPLC analysis: purity 79.1% (retention time: 2.998 min.) MS (ESI+): 499 (M+H)

Example 262

1-[2-methyl-3-(2-methyl-4-phenyl-5-oxazolyl)propanoyl]-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 45% HPLC analysis: purity 100% (retention time: 2.307 min.) MS (ESI+): 425 (M+H)

Example 263

1-[2,2-dimethyl-3-(2-methyl-4-phenyl-5-oxazolyl)propanoyl]-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 44% HPLC analysis: purity 100% (retention time: 2.350 min.) MS (ESI+): 439 (M+H)

Example 264

1-[(1-methyl-4-piperidinyl)methyl]-4-[3-(2-pentyl-4-phenyl-5-oxazolyl)propanoyl]piperazine bis trifluoroacetate

yield: 47% HPLC analysis: purity 95.1% (retention time: 2.898 min.) MS (ESI+): 467 (M+H)

Example 265

1-{3-[4-(4-chlorophenyl)-2-(propylsulfanyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 33% HPLC analysis: purity 77.8% (retention time: 3.105 min.) MS (ESI+): 505 (M+H)

Example 266

1-[(1-methyl-4-piperidinyl)methyl]-4-{3-[2-methyl-4-(5,6,7,8-tetrahydro-2-naphthalenyl)-5-oxazolyl]propanoyl}piperazine bis trifluoroacetate

yield: 22% HPLC analysis: purity 92.4% (retention time: 2.708 min.) MS (ESI+): 465 (M+H)

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Example 267

1-{3-[4-(4-chlorophenyl)-2-(4-methyl-1-piperazinyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 38% HPLC analysis: purity 91.7% (retention time: 2.198 min.) MS (ESI+): 529 (M+H)

Example 268

1-{3-[4-(4-chlorophenyl)-2-(1-pyrrolidinyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 43% HPLC analysis: purity 86.9% (retention time: 2.180 min.) MS (ESI+): 500 (M+H)

Example 269

1-{3-[4-(4-chlorophenyl)-2-(cyclohexylamino)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 27% HPLC analysis: purity 91.7% (retention time: 2.582 min.) MS (ESI+): 528 (M+H)

Example 270

1-(3-{4-(4-chlorophenyl)-2-[(2-pyridinylmethyl)sulfanyl]-5-oxazolyl}propanoyl)-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 44% HPLC analysis: purity 94.5% (retention time: 2.488 min.) MS (ESI+): 554 (M+H)

Example 271

1-(3-{4-(4-chlorophenyl)-2-[(4-methyl-pyrimidin-2-yl)sulfanyl]-5-oxazolyl}propanoyl)-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 33% HPLC analysis: purity 92.2% (retention time: 2.874 min.) MS (ESI+): 555 (M+H)

Example 272

1-(3-{4-(4-chlorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]-5-oxazolyl}propanoyl)-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 42% HPLC analysis: purity 90.6% (retention time: 2.566 min.) MS (ESI+): 544 (M+H)

Example 273

1-{3-[4-(4-chlorophenyl)-2-(2-isopropyl-1H-imidazol-1-yl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 45% HPLC analysis: purity 96.3% (retention time: 2.597 min.) MS (ESI+): 539 (M+H)

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Example 274

1-{3-[4-(4-chlorophenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 22% HPLC analysis: purity 86.3% (retention time: 3.028 min.) MS (ESI+): 525 (M+H)

Example 275

1-(3-(4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl)propanoyl)-4-[(1-methyl-4-piperidinyl)methyl]piperazine tris trifluoroacetate

yield: 38% HPLC analysis: purity 94.7% (retention time: 2.737 min.) MS (ESI+): 575 (M+H)

Example 276

1-(3-[2-(1,3-benzodioxol-5-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl)-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 18% HPLC analysis: purity 82.2% (retention time: 3.711 min.) MS (ESI+): 551 (M+H)

Example 277

1-{3-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 9% HPLC analysis: purity 92.9% (retention time: 3.003 min.) MS (ESI+): 521 (M+H)

Example 278

1-{3-[4-(4-chlorophenyl)-2-(2-naphthyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 14% HPLC analysis: purity 78.8% (retention time: 3.391 min.) MS (ESI+): 557 (M+H)

Example 279

1-{3-[4-(4-chlorophenyl)-2-(2-thienyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 43% HPLC analysis: purity 80.6% (retention time: 3.020 min.) MS (ESI+): 513 (M+H)

Example 280

1-{3-[4-(4-chlorophenyl)-2-propyl-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine bis trifluoroacetate

yield: 35% HPLC analysis: purity 94.4% (retention time: 2.825 min.) MS (ESI+): 473 (M+H)

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Example 281

3-[4-(4-chlorophenyl)-2-(1-naphthyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 13% HPLC analysis: purity 99.4% (retention time: 4.846 min.) MS (ESI+): 603 (M+H) NMR(CDCl₃) delta: 1.12–1.22 (6H, m), 2.29 (2H, t, J=7.5 Hz), 3.07 (2H, t, J=21.5 Hz), 3.47 (2H, t, J=7.5 Hz), 3.88–4.02 (4H, m), 7.12–7.22 (2H, m), 7.38–7.68 (7H, m), 7.81 (2H, d, J=9 Hz), 7.92 (2H, dd, J=13, 8 Hz), 8.16 (1H, d, J=7 Hz), 9.35 (1H, d, J=8.5 Hz)

Example 282

3-[4-(4-chlorophenyl)-2-(3,4-dichlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 22% HPLC analysis: purity 100% (retention time: 4.785 min.) MS (ESI+): 621 (M+H)

Example 283

3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 56% HPLC analysis: purity 99.7% (retention time: 4.395 min.) MS (ESI+): 606 (M+H)

Example 284

3-[4-(4-chlorophenyl)-2-(1H-indazol-3-yl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 35% HPLC analysis: purity 98.8% (retention time: 4.216 min.) MS (ESI+): 593 (M+H)

Example 285

1-{3-[4-(4-chlorophenyl)-2-(1-naphthyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 48% HPLC analysis: purity 99.0% (retention time: 4.428 min.) MS (ESI+): 461 (M+H)

Example 286

1-{3-[4-(4-chlorophenyl)-2-(3,4-dichlorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 39% HPLC analysis: purity 99.4% (retention time: 4.358 min.) MS (ESI+): 479 (M+H)

Example 287

1-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 45% HPLC analysis: purity 99.7% (retention time: 3.939 min.) MS (ESI+): 464 (M+H) NMR (CDCl₃) delta: 1.40–1.52 (2H, m), 1.80–1.92 (2H, m), 2.87 (2H, t, J=7.5Hz), 3.18–3.30 (2H, m), 3.36 (2H, t, J=7.5 Hz), 3.66–3.80 (2H, m), 3.91 (3H, s), 4.00–4.10 (1H, m),

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7.30–7.46 (3H, m), 7.45 (2H, d, J=8.5 Hz) 7.71 (2H, d, J=8.5 Hz), 8.15 (1H, s), 8.18(1H, d, J=7 Hz)

Example 288

1-{3-[4-(4-chlorophenyl)-2-(1H-indazol-3-yl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 4% HPLC analysis: purity 100% (retention time: 3.719 min.) MS (ESI+): 451 (M+H)

Example 289

4-{3-[4-(4-chlorophenyl)-2-(1-naphthyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 9% HPLC analysis: purity 100% (retention time: 4.595 min.) MS (ESI+): 495 (M+H)

Example 290

4-{3-[4-(4-chlorophenyl)-2-(3,4-dichlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 16% HPLC analysis: purity 100% (retention time: 4.530 min) MS (ESI+): 513 (M+H)

Example 291

4-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 54% HPLC analysis: purity 99.5% (retention time: 4.166 min.) MS (ESI+): 498 (M+H)

Example 292

4-{3-[4-(4-chlorophenyl)-2-(1H-indazol-3-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 44% HPLC analysis: purity 100% (retention time: 3.977 min.) MS (ESI+): 485 (M+H)

Example 293

1-{3-[4-(4-chlorophenyl)-2-(1-naphthyl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine

yield: 59% HPLC analysis: purity 99.7% (retention time: 3.413 min.) MS (ESI+): 557 (M+H)

Example 294

1-(3-[4-(4-chlorophenyl)-2-(3,4-dichlorophenyl)-5-oxazolyl]propanoyl)-4-[(1-methyl-4-piperidinyl)methyl]piperazine

yield: 61% HPLC analysis: purity 99.9% (retention time: 3.347 min.) MS (ESI+): 575 (M+H)

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Example 295

1-(3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propanoyl)-4-[(1-methyl-4-piperidinyl)methyl]piperazine

yield: 45% HPLC analysis: purity 100% (retention time: 3.188 min.) MS (ESI+): 560 (M+H)

Example 296

1-{3-[4-(4-chlorophenyl)-2-(1H-indazol-3-yl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidinyl)methyl]piperazine

yield: 3% HPLC analysis: purity 100% (retention time: 3.141 min.) MS (ESI+): 547 (M+H)

Example 297

To a solution of diethyl bromodifluoromethylphosphonate (4.8 g) in N,N-dimethylacetamide (9 ml) was added zinc powder (1.17 g) under a nitrogen stream and the reaction mixture was stirred at room temperature for 2 hrs. Insoluble material was filtered off and copper(I) bromide (2.58 g) was added to the filtrate under a nitrogen stream. After stirring the reaction mixture at room temperature for 30 min, tert-butyl 4-iodophenylcarbamate (2.87 g) was added, and the mixture was stirred overnight. Ethyl acetate was added to the reaction mixture and the insoluble material was filtered off. The filtrate was concentrated, introduced into preparative HPLC and purified. Ethyl acetate was added and 4N hydrochloric acid ethyl acetate solution (3 ml) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated and crystals were collected by filtration to give diethyl α,α -difluoro-4-amino-benzylphosphonate hydrochloride (250 mg, yield 10%).

A mixture of the obtained hydrochloride (100 mg), 3-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (30 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (22 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (29 mg) and N,N-dimethylformamide (0.5 ml) was stirred overnight at room temperature. To the reaction mixture was added 0.1N aqueous hydrochloric acid solution (1 ml) and the reaction mixture was extracted with ethyl acetate (2 ml). The organic layer was concentrated, introduced into preparative HPLC and purified to give 3-[2-(1H-benzoimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(diethylphosphono)(difluoro)methyl]phenyl}propionamide (51.4 mg, yield 50%). Recrystallization from ethyl acetate-isopropyl ether gave yellow prism crystals. melting point: 155–156° C.

Example 298

A mixture of diethyl 4-amino- α -hydroxybenzylphosphonate (50 mg), 3-{3-[2-(1H-benzoimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (54 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (38 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (43 mg) and N,N-dimethylformamide (0.5 ml) was stirred overnight at room temperature. To the reaction mixture was added 0.1N aqueous hydrochloric acid solution (2 ml) and the reaction mixture was extracted with ethyl acetate (2 ml). The organic layer was concentrated, introduced into preparative HPLC and purified to give 3-[2-(1H-benzoimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-[(diethylphosphono)(hy-

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droxy)methyl]phenyl}propionamide (52 mg, 58%). Recrystallization from ethyl acetate-isopropyl ether gave yellow prism crystals. melting point: 171–172° C. MS (ESI+): 609 (M+H)

In the same manner as in Example 298, the compounds of Examples 299–342 were synthesized.

Example 299

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(diethylphosphono)(methoxy)methyl]phenyl}propionamide

yield: 65%. colorless prism crystals, melting point: 191–192° C. (recrystallized from ethyl acetate-isopropyl ether).

MS (ESI+): 623 (M+H)

Example 300

1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-3-piperidinol

yield 81%. colorless prism crystals, melting point: 104–105° C. (recrystallized from ethyl acetate-isopropyl ether).

MS (ESI+): 451 (M+H)

Example 301

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(ethylsulfonyl)ethyl]propanamide

yield 54%. colorless prism crystals, melting point: 182–183° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 487 (M+H)

Example 302

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(methylsulfonyl)ethyl]propanamide was obtained.

yield 62%. colorless prism crystals, melting point: 194–195° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 473 (M+H)

Example 303

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[2-(methylsulfonyl)ethyl]-N-methylpropanamide

yield 85%. colorless prism crystals, melting point: 141–142° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 487 (M+H)

Example 304

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(4-hydroxycyclohexyl)propanamide

yield 70%. colorless prism crystals, melting point: 204–206° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 465 (M+H)

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Example 305

(1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-piperidiny)methanol

yield 86%. yellow prism crystals, melting point: 101–102° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 465 (M+H)

Example 306

1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-bromopiperidine

yield 78%. colorless prism crystals, melting point: 116–117° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 514 (M+H)

Example 307

1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-(methylsulfonyl)piperidine

yield 80%. colorless prism crystals, melting point: 215–216° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 513 (M+H)

Example 308

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-(1,1-dioxidetetrahydro-2H-thiopyran-4-yl)propanamide

yield 52%. yellow prism crystal, melting point: 236–238° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 499 (M+H)

Example 309

4-{3-[2-(1H-benzimidazol-1-yl)-4-chlorophenyl-5-oxazolyl]propanoyl}1,4-thiazepan-1,1'-dioxide

yield 90%. yellow prism crystals, melting point: 142–144° C. (recrystallized from ethyl acetate-isopropyl ether). MS (ESI+): 499 (M+H)

Example 310

1-(3-{4-phenyl-2-[(E)-2-phenylethenyl]-5-oxazolyl}propanoyl)-4-piperidinol

yield: 27% HPLC analysis: purity 83.5% (retention time: 3.792 min.) MS (ESI+): 403 (M+H)

Example 311

1-{3-[4-(4-chlorophenyl)-2-(propylsulfanyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 49% HPLC analysis: purity 98.6% (retention time: 4.009 min.) MS (ESI+): 409 (M+H)

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Example 312

1-{3-[4-(4-chlorophenyl)-2-(1-methylcyclohexyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 39% HPLC analysis: purity 96.3% (retention time: 4.360 min.) MS (ESI+): 431 (M+H)

Example 313

1-{3-[4-(4-chlorophenyl)-2-(cyclohexylsulfanyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 61% HPLC analysis: purity 96.6% (retention time: 4.491 min.) MS (ESI+): 449 (M+H)

Example 314

1-(3-{4-(4-chlorophenyl)-2-[(2-pyridinylmethyl)sulfanyl]-5-oxazolyl}propanoyl)-4-piperidinol

yield: 21% HPLC analysis: purity 94.8% (retention time: 2.909 min.) MS (ESI+): 458 (M+H)

Example 315

1-{3-[4-(4-chlorophenyl)-2-(2-isopropyl-1H-imidazol-1-yl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 82% HPLC analysis: purity 95.7% (retention time: 3.013 min.) MS (ESI+): 443 (M+H)

Example 316

1-(3-{4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl}propanoyl)-4-piperidinol

yield: 35% HPLC analysis: purity 96.3% (retention time: 3.316 min.) MS (ESI+): 479 (M+H)

Example 317

1-{3-[4-(4-chlorophenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 44% HPLC analysis: purity 97.5% (retention time: 3.760 min.) MS (ESI+): 429 (M+H)

Example 318

1-{3-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 7% HPLC analysis: purity 91.1% (retention time: 3.806 min.) MS (ESI+): 425 (M+H)

Example 319

1-{3-[4-(4-chlorophenyl)-2-(2-thienyl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 12% HPLC analysis: purity 93.5% (retention time: 3.873 min.) MS (ESI+): 417 (M+H)

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Example 320

1-{3-[4-(4-chlorophenyl)-2-propyl-5-oxazolyl]propanoyl}-4-piperidinol

yield: 25% HPLC analysis: purity 97.2% (retention time: 3.544 min.) MS (ESI+): 377 (M+H)

Example 321

4-(3-(4-phenyl-2-[(E)-2-phenylethenyl]-5-oxazolyl)propanoyl)thiomorpholine-1,1-dioxide

yield: 40% HPLC analysis: purity 99.0% (retention time: 4.038 min.) MS (ESI+): 437 (M+H)

Example 322

4-{3-[4-(4-chlorophenyl)-2-(propylsulfanyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 48% HPLC analysis: purity 100% (retention time: 4.285 min.) MS (ESI+): 443 (M+H)

Example 323

4-{3-[4-(4-chlorophenyl)-2-(1-methylcyclohexyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 47% HPLC analysis: purity 100% (retention time: 4.588 min.) MS (ESI+): 465 (M+H)

Example 324

4-{3-[4-(4-chlorophenyl)-2-(cyclohexylsulfanyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 31% HPLC analysis: purity 100% (retention time: 4.689 min.) MS (ESI+): 483 (M+H)

Example 325

4-{3-[4-(4-chlorophenyl)-2-(cyclohexylamino)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 35% HPLC analysis: purity 87.6% (retention time: 3.209 min.) MS (ESI+): 466 (M+H)

Example 326

4-(3-{4-(4-chlorophenyl)-2-[(2-pyridinylmethyl)sulfanyl]-5-oxazolyl}propanoyl)thiomorpholine-1,1-dioxide

yield: 42% HPLC analysis: purity 99.8% (retention time: 3.073 min.) MS (ESI+): 492 (M+H)

Example 327

4-(3-{4-(4-chlorophenyl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)sulfanyl]-5-oxazolyl}propanoyl)thiomorpholine-1,1-dioxide

yield: 32% HPLC analysis: purity 99.8% (retention time: 3.204 min.) MS (ESI+): 482 (M+H)

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Example 328

4-{3-[4-(4-chlorophenyl)-2-(2-isopropyl-1H-imidazol-1-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 59% HPLC analysis: purity 100% (retention time: 3.171 min.) MS (ESI+): 477 (M+H)

Example 329

4-(3-{4-(4-chlorophenyl)-2-[2-(hydroxymethyl)-1H-imidazol-1-yl]-5-oxazolyl}propanoyl)thiomorpholine-1,1-dioxide

yield: 19% HPLC analysis: purity 99.6% (retention time: 2.893 min.) MS (ESI+): 465 (M+H)

Example 330

4-{3-[2-(4-tert-butylphenoxy)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 28% HPLC analysis: purity 93.1% (retention time: 4.856 min.) MS (ESI+): 517 (M+H)

Example 331

4-(3-{4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl}propanoyl)thiomorpholine-1,1-dioxide

yield: 14% HPLC analysis: purity 100% (retention time: 3.559 min.) MS (ESI+): 513 (M+H)

Example 332

4-{3-[4-(4-chlorophenyl)-2-(4-methyl-1-piperazinyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 25% HPLC analysis: purity 88.3% (retention time: 2.754 min.) MS (ESI+): 467 (M+H)

Example 333

4-{3-[4-(4-chlorophenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 39% HPLC analysis: purity 100% (retention time: 4.033 min.) MS (ESI+): 463 (M+H)

Example 334

4-{3-[2-benzyl-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 50% HPLC analysis: purity 99.8% (retention time: 4.043 min.) MS (ESI+): 459 (M+H)

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Example 335

4-{3-[4-(4-chlorophenyl)-2-(2-thienyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide

yield: 31% HPLC analysis: purity 99.0% (retention time: 4.115 min.) MS (ESI+): 451 (M+H)

Example 336

4-(3-[4-(4-chlorophenyl)-2-propyl-5-oxazolyl]propanoyl)thiomorpholine-1,1-dioxide

yield: 25% HPLC analysis: purity 100% (retention time: 3.816 min.) MS (ESI+): 411 (M+H)

Example 337

3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-2-yl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 48% HPLC analysis: purity 100% (retention time: 4.958 min.) MS (ESI+): 606 (M+H)

Example 338

3-[4-(4-chlorophenyl)-2-(1H-indazol-1-yl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide

yield: 78% HPLC analysis: purity 99.7% (retention time: 4.576 min.) MS (ESI+): 593 (M+H)

Example 339

4-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-2-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 73% HPLC analysis: purity 100% (retention time: 4.724 min.) MS (ESI+): 498 (M+H)

Example 340

4-{3-[4-(4-chlorophenyl)-2-(1H-indazol-1-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1'-dioxide

yield: 71% HPLC analysis: purity 93.8% (retention time: 4.347 min.) MS (ESI+): 485 (M+H)

Example 341

1-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-2-yl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 51% HPLC analysis: purity 99.2% (retention time: 4.374 min.) MS (ESI+): 464 (M+H)

Example 342

1-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-2-yl)-5-oxazolyl]propanoyl}-4-piperidinol

yield: 65% HPLC analysis: purity 98.9% (retention time: 4.067 min.) MS (ESI+): 451 (M+H)

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Example 343

To a mixture of 3-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiazolidine (25 mg) and tetrahydrofuran (10 mL) was added m-chloroperbenzoic acid (14.4 mg) with stirring under ice-cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate and then with saturated brine, dried (MgSO₄) and concentrated. The residue was introduced into preparative HPLC and purified to give 3-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiazolidine-1-oxide (7.3 mg, yield 28%).

HPLC analysis: purity 98.5% (retention time: 3.628 min.)
MS (ESI+): 455 (M+H)

Example 344

To a mixture of 3-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiazolidine (25 mg) and tetrahydrofuran (10 mL) was added m-chloroperbenzoic acid (28.8 mg) with stirring under ice-cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate and then with saturated brine, dried (MgSO₄) and concentrated. The residue was introduced into preparative HPLC and purified to give 3-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiazolidine-1,1-dioxide (10.7 mg, yield 40%). Recrystallization from ethyl acetate-hexane gave yellow prism crystals. melting point: 136–137° C.

HPLC analysis: purity 94.8% (retention time: 4.053 min.)
MS (ESI+): 471 (M+H)

Example 345

A mixture of 4-[(diethylphosphono)(fluoro)methyl]nitrobenzene (74 mg), 10% Pd—C (10 mg) and ethanol (2 ml) was stirred at room temperature under a hydrogen stream for 1 hr. Pd—C was removed from the reaction mixture by filtration and the filtrate was concentrated. To the residue were added 3-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propionic acid (25 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (20 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (27 mg) and N,N-dimethylformamide (0.5 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was concentrated, introduced into preparative HPLC and purified to give 3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(diethylphosphono)(fluoro)methyl]phenyl}propionamide. Recrystallization from ethyl acetate-isopropyl ether gave colorless prism crystals (5 mg, yield 12%). melting point: 152–155° C.

MS (ESI+): 611 (M+H)

Example 346

A mixture of 3-[4-(4-chlorophenyl)-2-propyl-5-oxazolyl]propionic acid (41.7 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (41 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (46 mg), 4-[(1-methyl-4-piperidiny)methyl]

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piperazine (60 mg) and N,N-dimethylformamide (0.5 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was concentrated, introduced into preparative HPLC and purified. To the obtained oil was added ethyl acetate, and the mixture was washed with saturated aqueous sodium hydrogen carbonate. A 4N hydrochloric acid ethyl acetate solution was added to the ethyl acetate layer and the mixture was concentrated to give 1-{3-[4-(4-chlorophenyl)-2-propyl-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidiny)methyl]piperazine dihydrochloride (25.0 mg, yield 32%). Recrystallization from ethanol-isopropyl ether gave colorless prism crystals. melting point: 218° c (dec.).

MS (ESI+): 473 (M+H)

Example 347

A mixture of 3-[4-(4-chlorophenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-oxazolyl]propionic acid (51.5 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (41 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (46 mg), 4-[(1-methyl-4-piperidiny)methyl]piperazine (60 mg) and N,N-dimethylformamide (0.5 ml) was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was concentrated, introduced into preparative HPLC and purified. Ethyl acetate was added to the obtained oil and the mixture was washed with saturated aqueous sodium hydrogen carbonate. The ethyl acetate layer was washed with saturated brine, dried (MgSO₄), and concentrated to give 1-{3-[4-(4-chlorophenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-oxazolyl]propanoyl}-4-[(1-methyl-4-piperidiny)methyl]piperazine (54.5 mg, yield 72%). Recrystallization from ethanol-isopropyl ether gave colorless prism crystals. melting point: 126–127° c.

MS (ESI+): 525 (M+H)

Example 348

A mixture of 3-[4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl]propionic acid (50 mg), 1-hydroxy-7-aza-1H-1,2,3-benzotriazole (41 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (46 mg), 4-[(1-methyl-4-piperidiny)methyl]piperazine (60 mg) and N,N-dimethylformamide (0.5 ml) was stirred overnight at room temperature. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was concentrated, introduced into preparative HPLC and purified. Ethyl acetate was added to the obtained oil and the mixture was washed with saturated aqueous sodium hydrogen carbonate. A 4N hydrochloric acid ethyl acetate solution was added to the ethyl acetate layer and the mixture was concentrated to give 1-(3-[4-(4-chlorophenyl)-2-[2-(methylsulfonyl)-1H-imidazol-1-yl]-5-oxazolyl]propanoyl)-4-[(1-methyl-4-piperidiny)methyl]piperazine 3 hydrochloric acid (65.0 mg, yield 66%).

HPLC analysis: purity 100% (retention time: 2.737 min.)
MS (ESI+): 575 (M+H)

Example 349

A mixture of 2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolepropionic acid (19 mg), (S)-3-(N-Boc-amino)pyrrolidine (10 mg), 1-hydroxybenzotriazole (8 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (10 mg) and N,N-dimethylformamide (1 ml) was

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shaken at room temperature for 8 hrs. The reaction mixture was poured into water, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was filtered and concentrated. The residue was dissolved in 4N hydrochloric acid ethyl acetate solution, left standing for 5 min. and concentrated. To the residue were added benzoic acid (10 mg), 1-hydroxy-7-azabenzotriazole (8 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (10 mg) and N,N-dimethylformamide (1 ml), and the mixture was shaken at room temperature for 16 hrs. The reaction mixture

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was directly introduced into preparative HPLC and purified to give the object compound.

Examples 350–394

In the same manner as in Example 349, the object compounds were obtained.

The structure and purity of the object compounds of Examples 349–394 were confirmed by LC-MS, HPLC. The yield, structure, purity and mass spectrum data of the object compounds are shown in [Table 1-1]–[Table 1-4].

TABLE 1-1

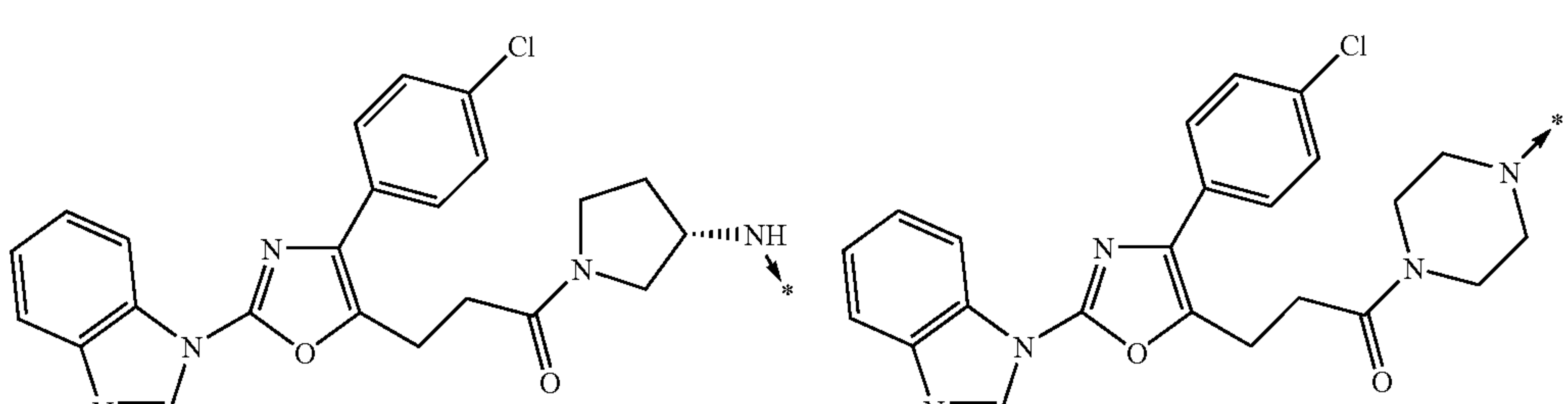
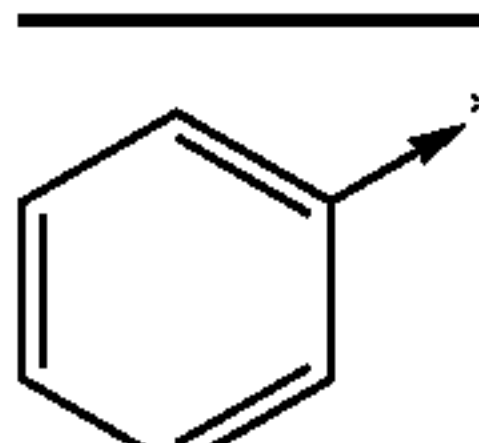
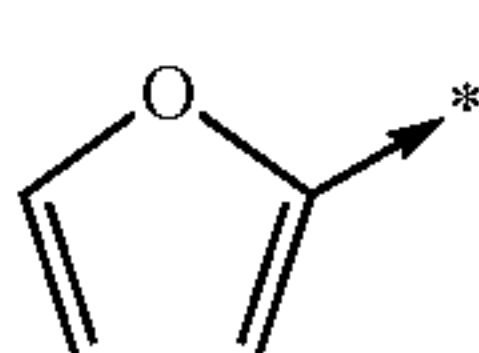
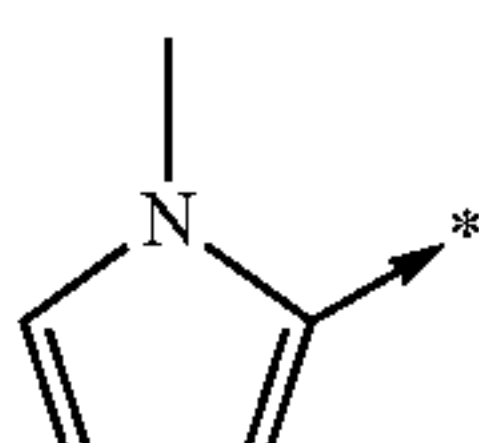
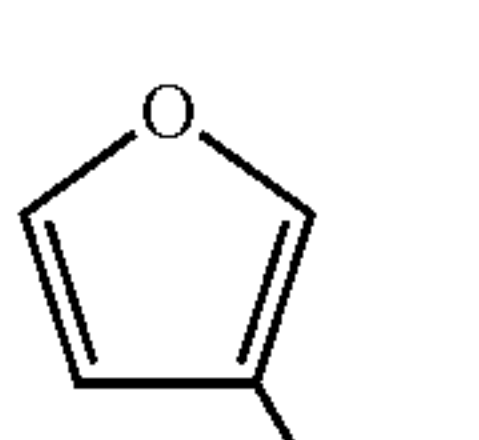
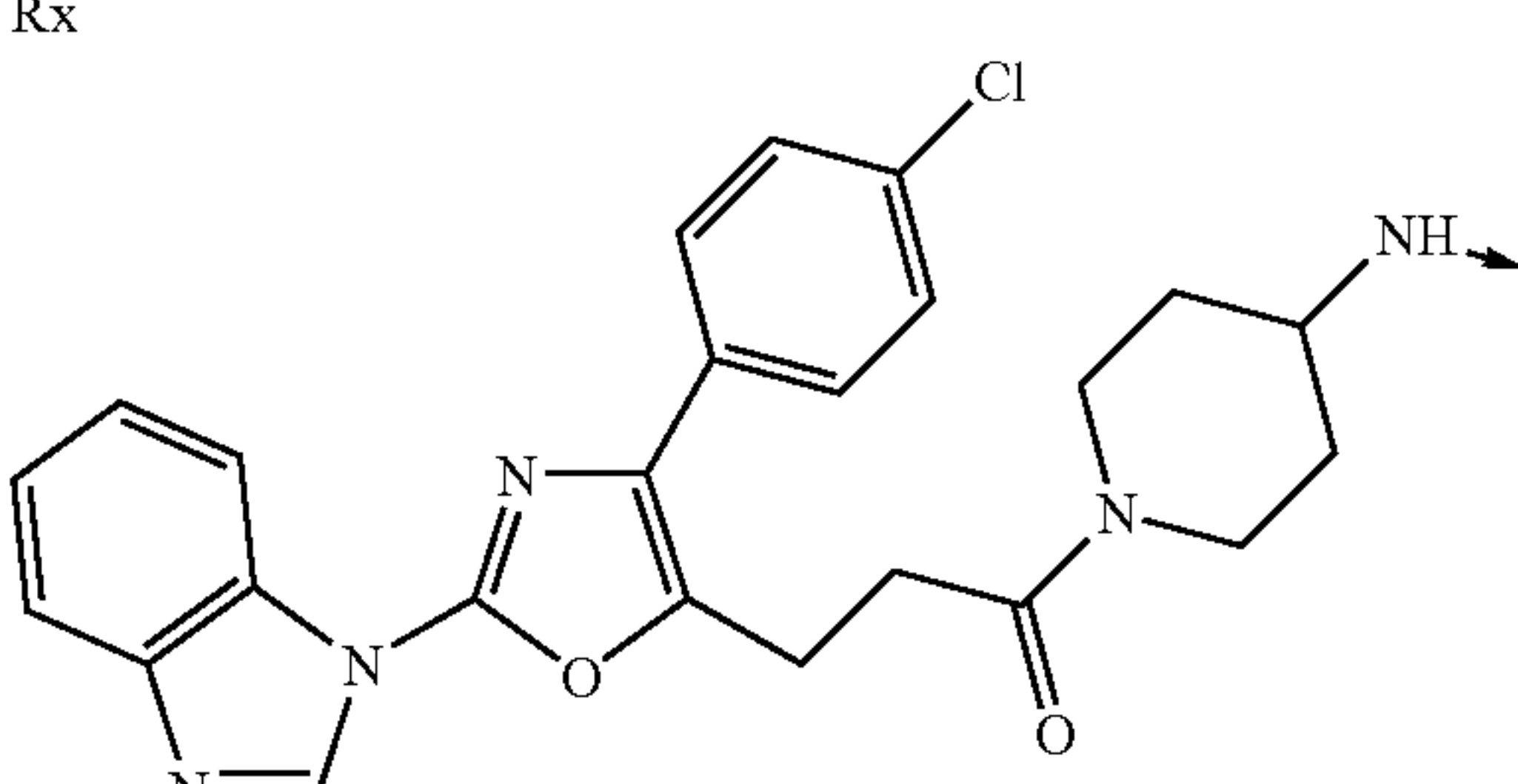
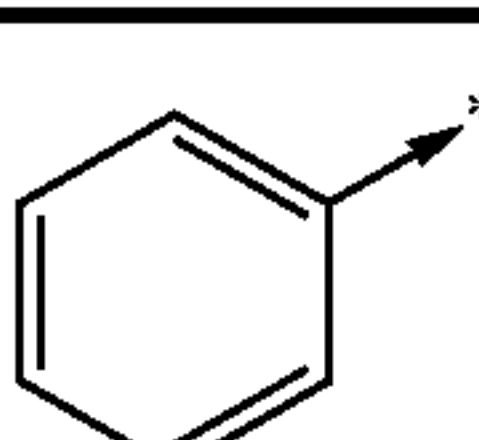
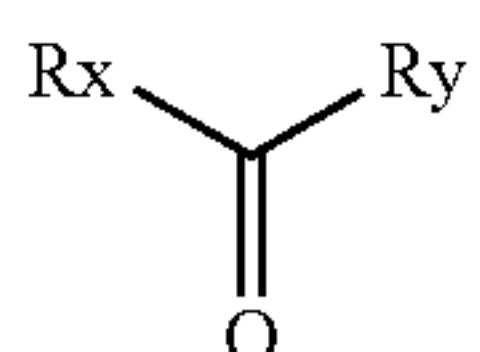
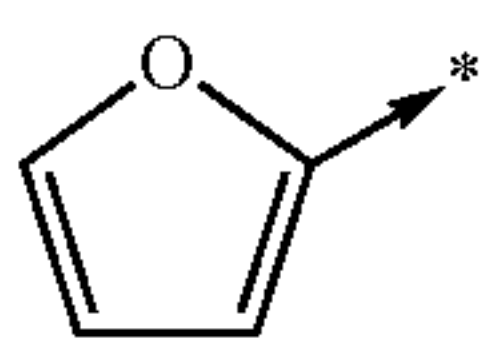
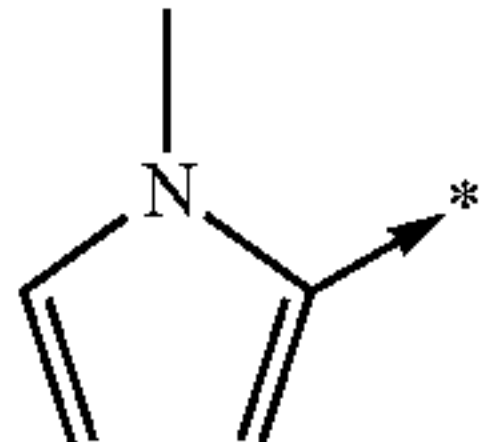
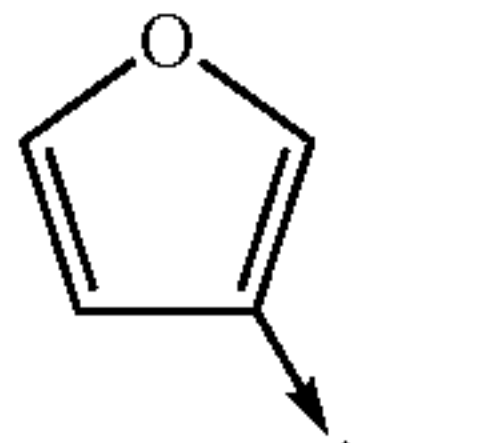
basic structure	
$\text{Rx} \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \\ \text{O} \end{array} \text{Ry}$	
	Rx
Ry	
	
	Example 349 19.5 mg, 99% 540 (M + 1)
	Example 354 16.6 mg, 99% 530 (M + 1)
	Example 360 16.9 mg, 99% 543 (M + 1)
	Example 366 15.1 mg, 99% 530 (M + 1)
	Rx
	
	Example 351 19.4 mg, 99% 554 (M + 1)

TABLE 1-1-continued

basic structure	
	
	Example 356 14.4 mg, 98% 544 (M + 1)
	Example 362 14.3 mg, 98% 557 (M + 1)
	Example 368 15.9 mg, 95% 544 (M + 1)

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 1-2

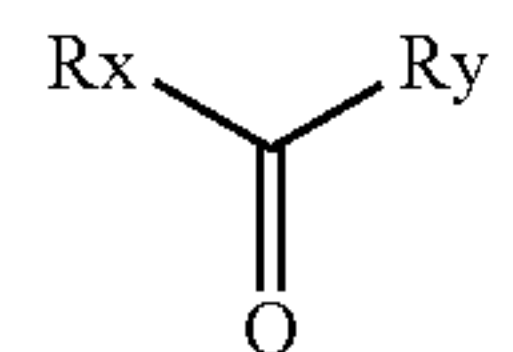
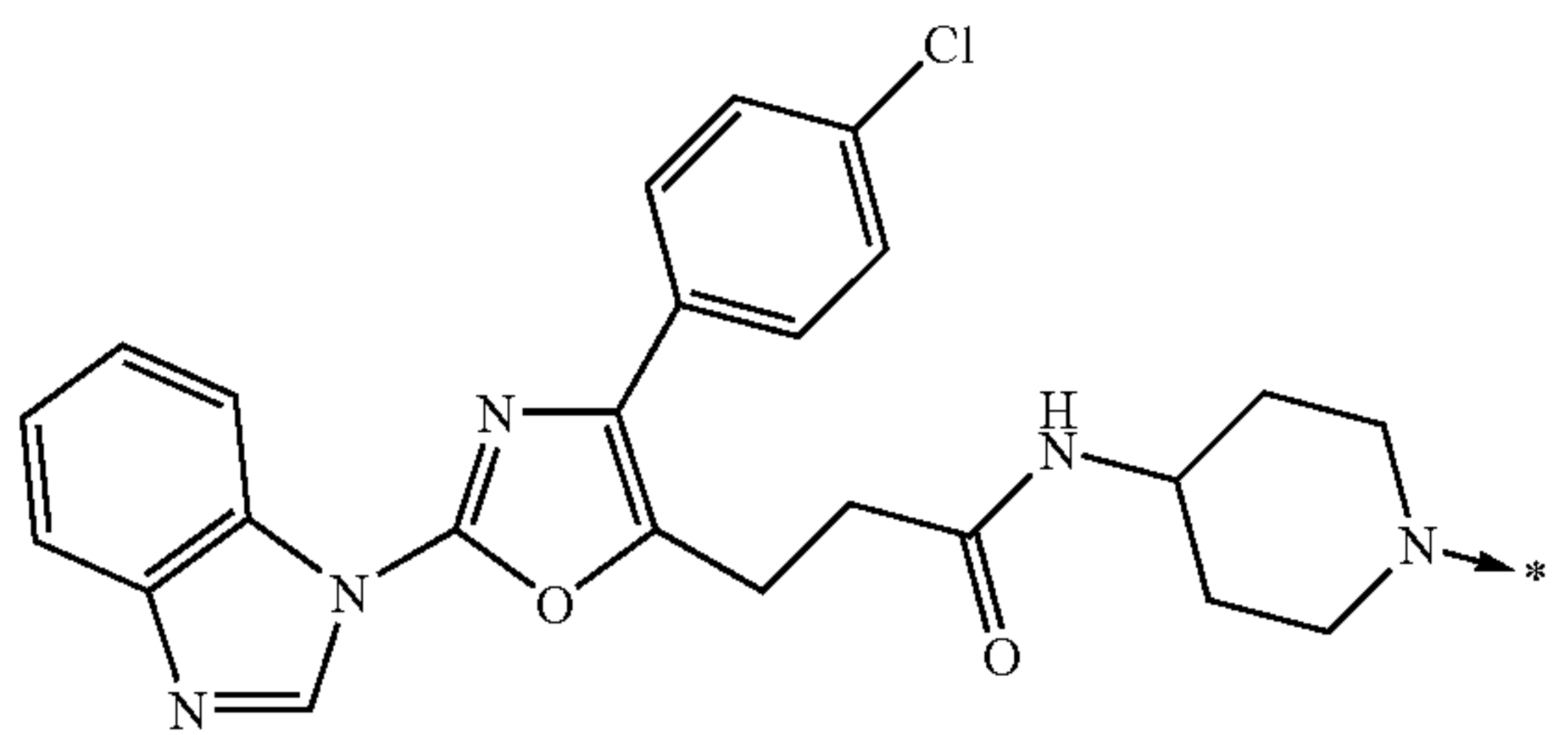
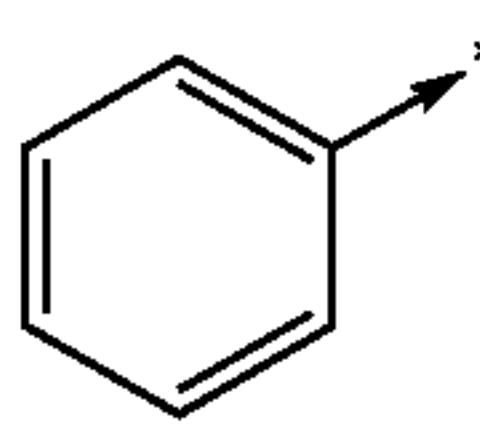
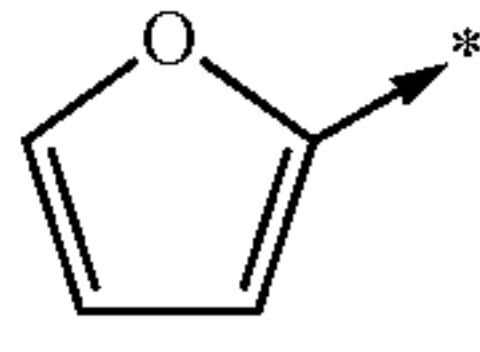
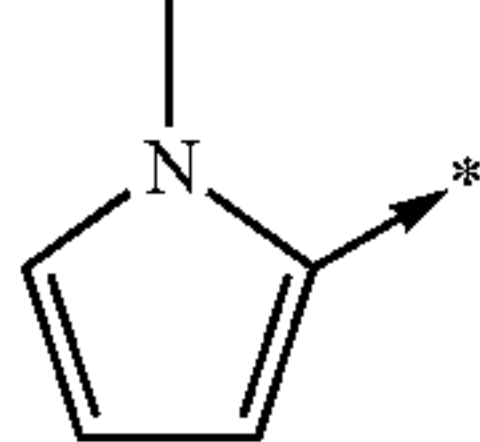
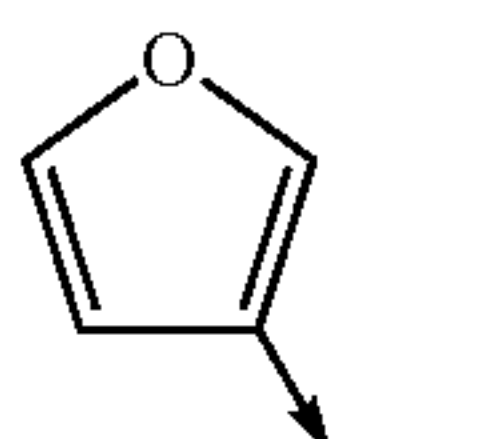
basic structure	
	
Ry	Rx
	
	
	Example 357 3.1 mg, 98% 544 (M + 1)
	Example 363 14.3 mg, 95% 557 (M + 1)
	Example 369 6.7 mg, 95% 544 (M + 1)

TABLE 1-2-continued

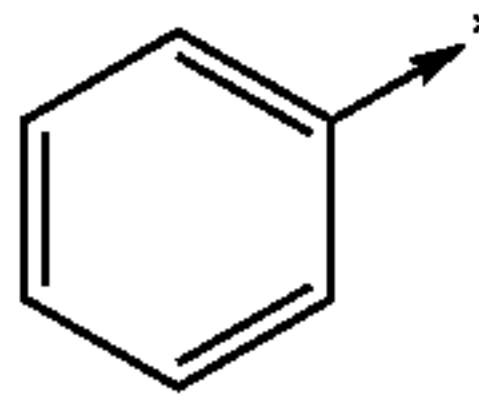
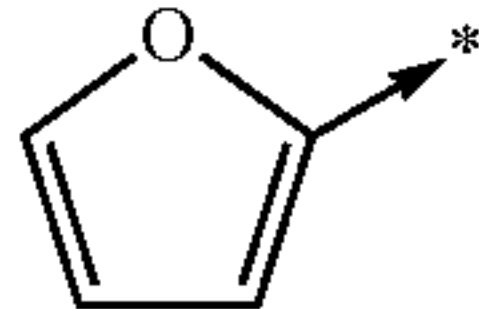
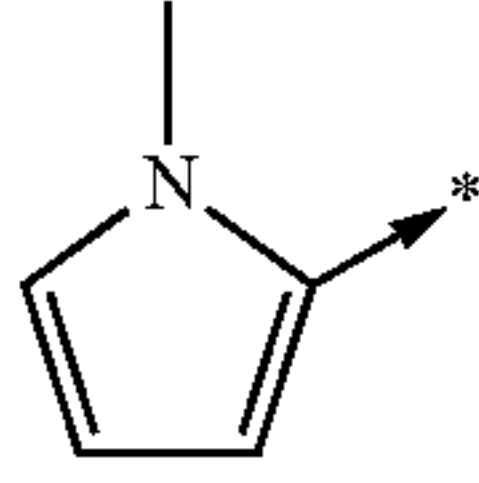
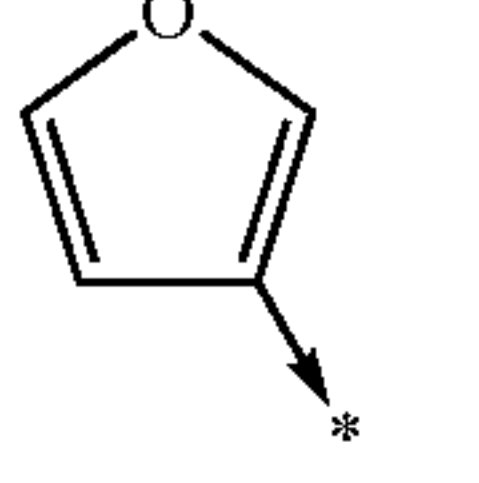
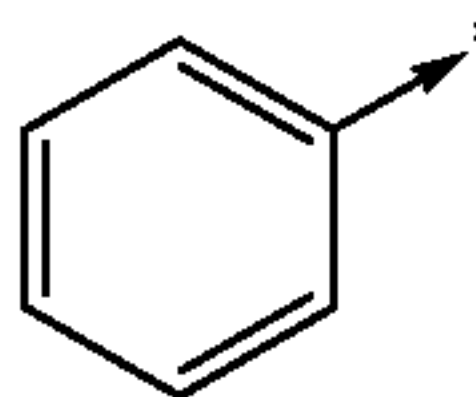
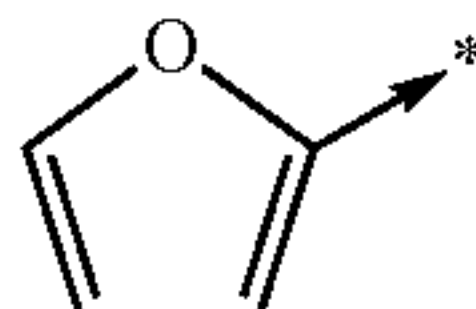
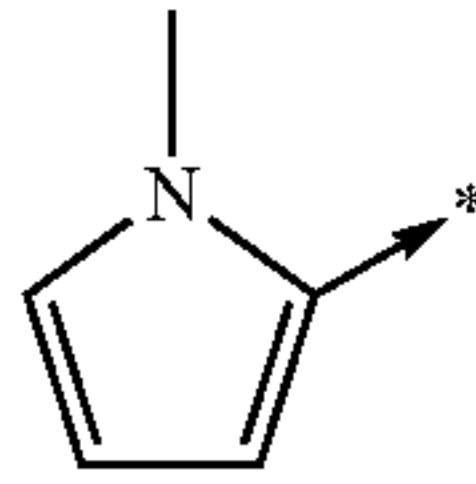
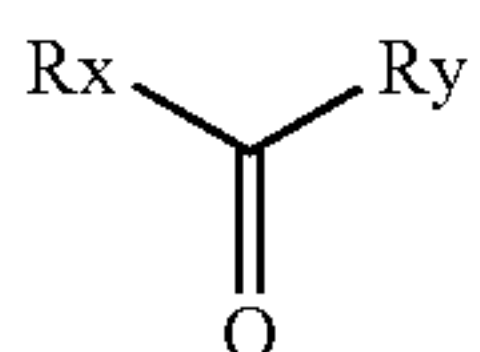
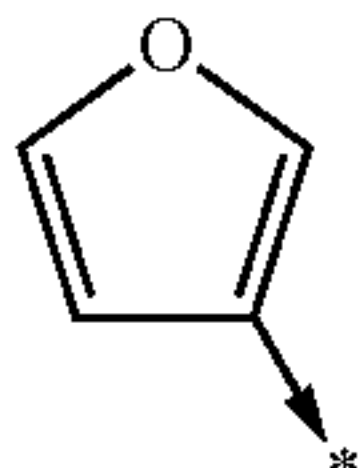
basic structure	
	$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$
Ry	Rx
	<p>Example 352 15.3 mg, 95% 542 (M + 1)</p>
	<p>Example 358 16.8 mg, 99% 532 (M + 1)</p>
	<p>Example 364 16.2 mg, 95% 545 (M + 1)</p>
	<p>Example 370 16.4 mg, 98% 532 (M + 1)</p>
Ry	Rx
	<p>Example 353 23.2 mg, 99% 514 (M + 1)</p>
	<p>Example 359 18.1 mg, 99% 504 (M + 1)</p>
	<p>Example 365 18.2 mg, 97% 517 (M + 1)</p>

TABLE 1-2-continued

basic structure	
	
	Example 371 12.2 mg, 98% 504 (M + 1)

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 1-3

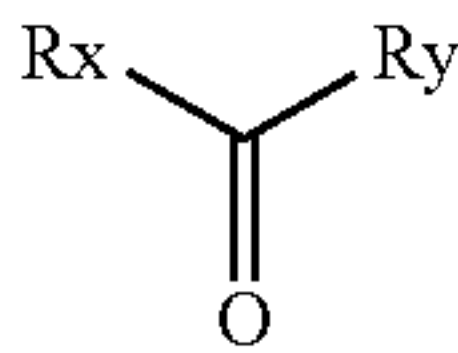
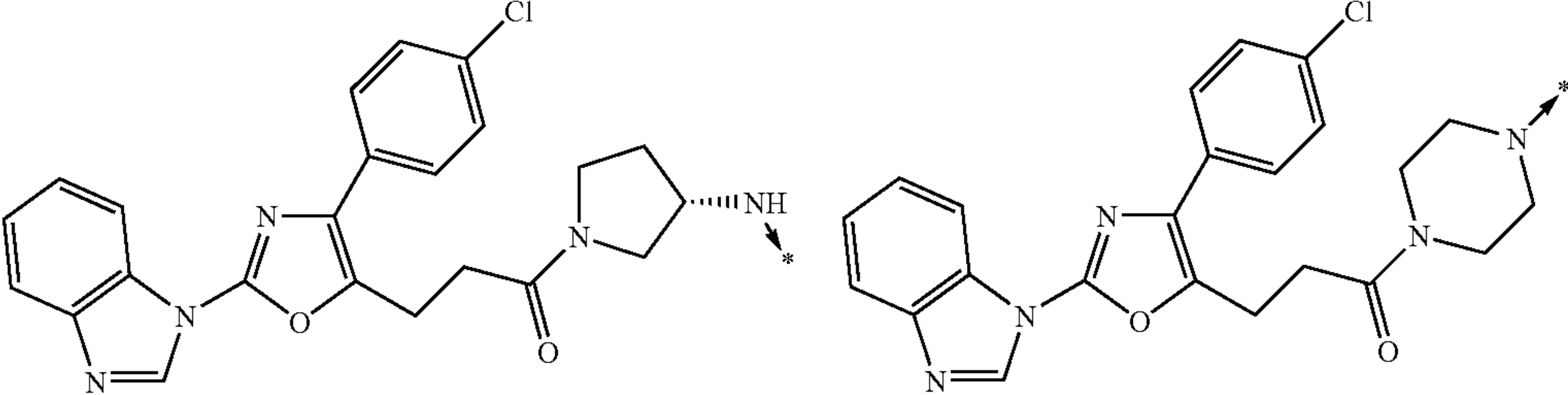
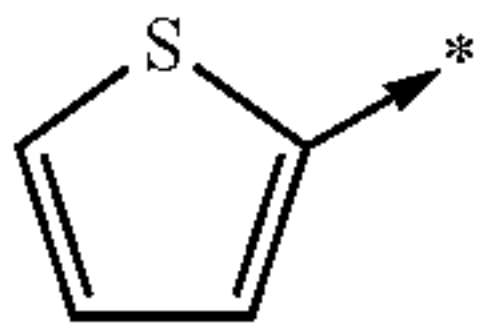
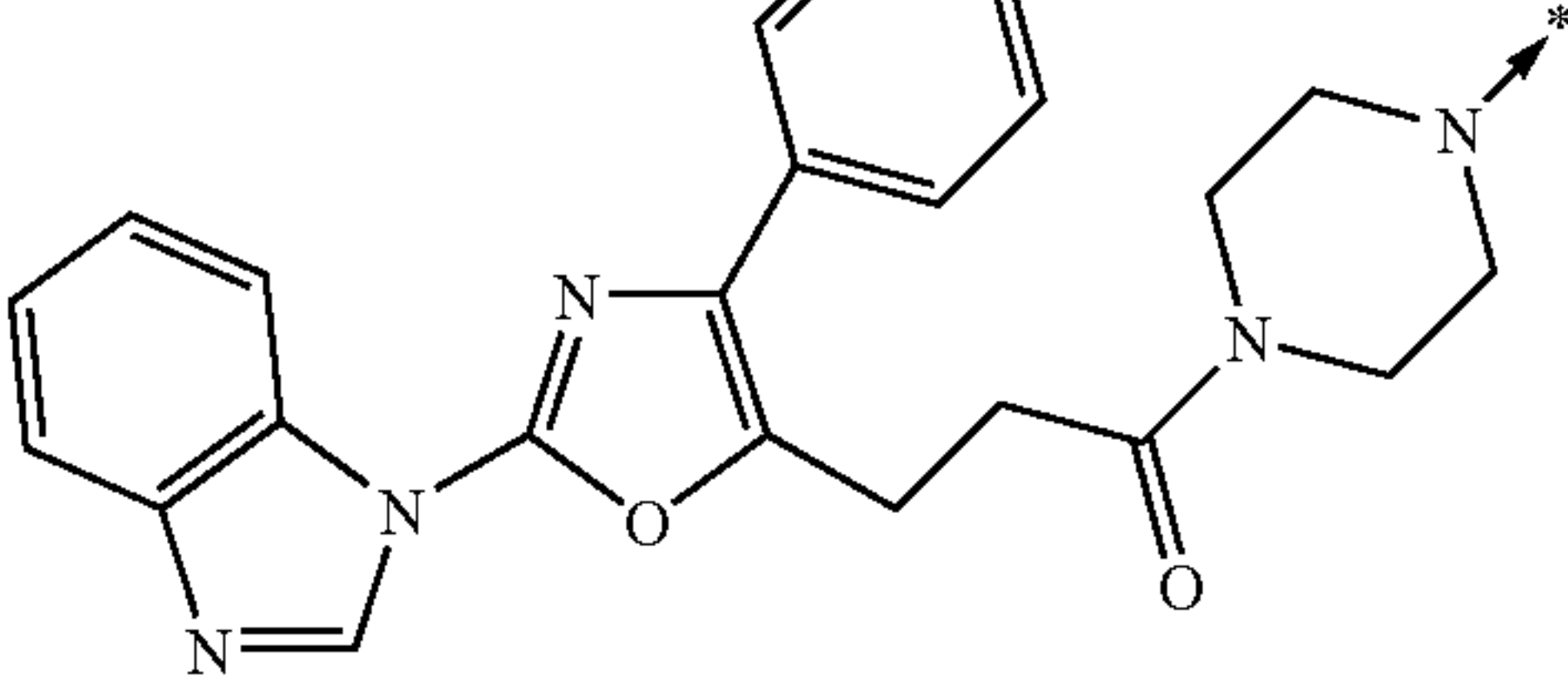
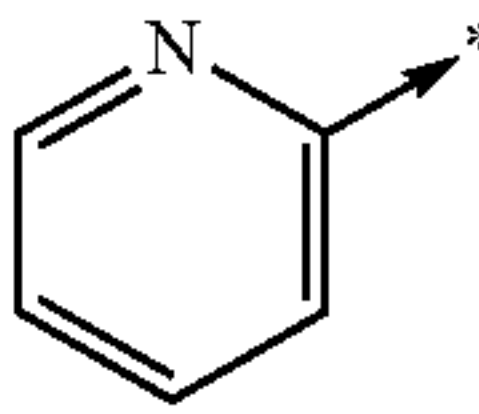
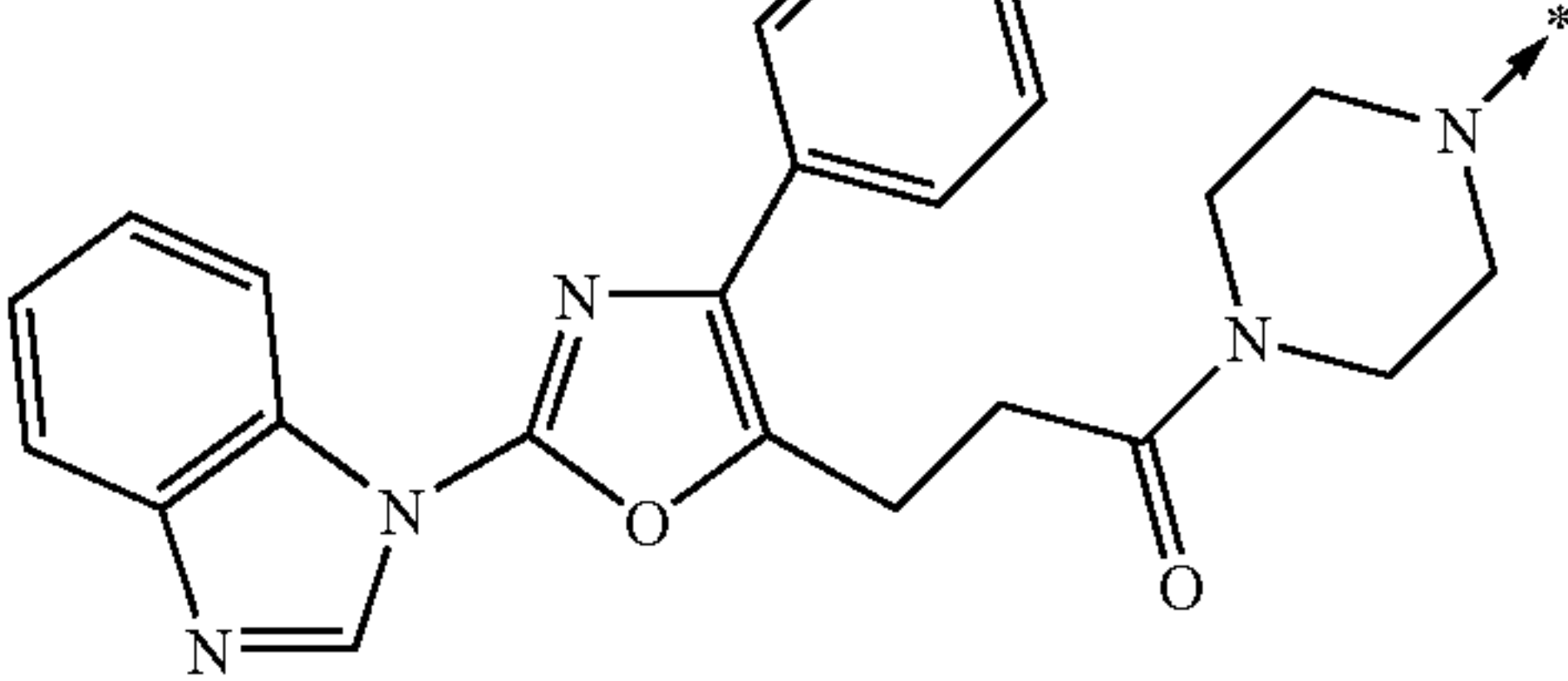
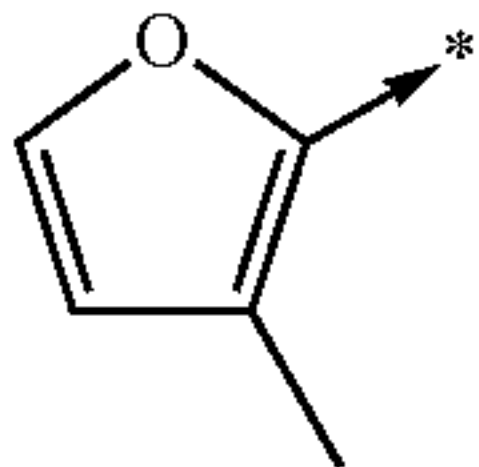
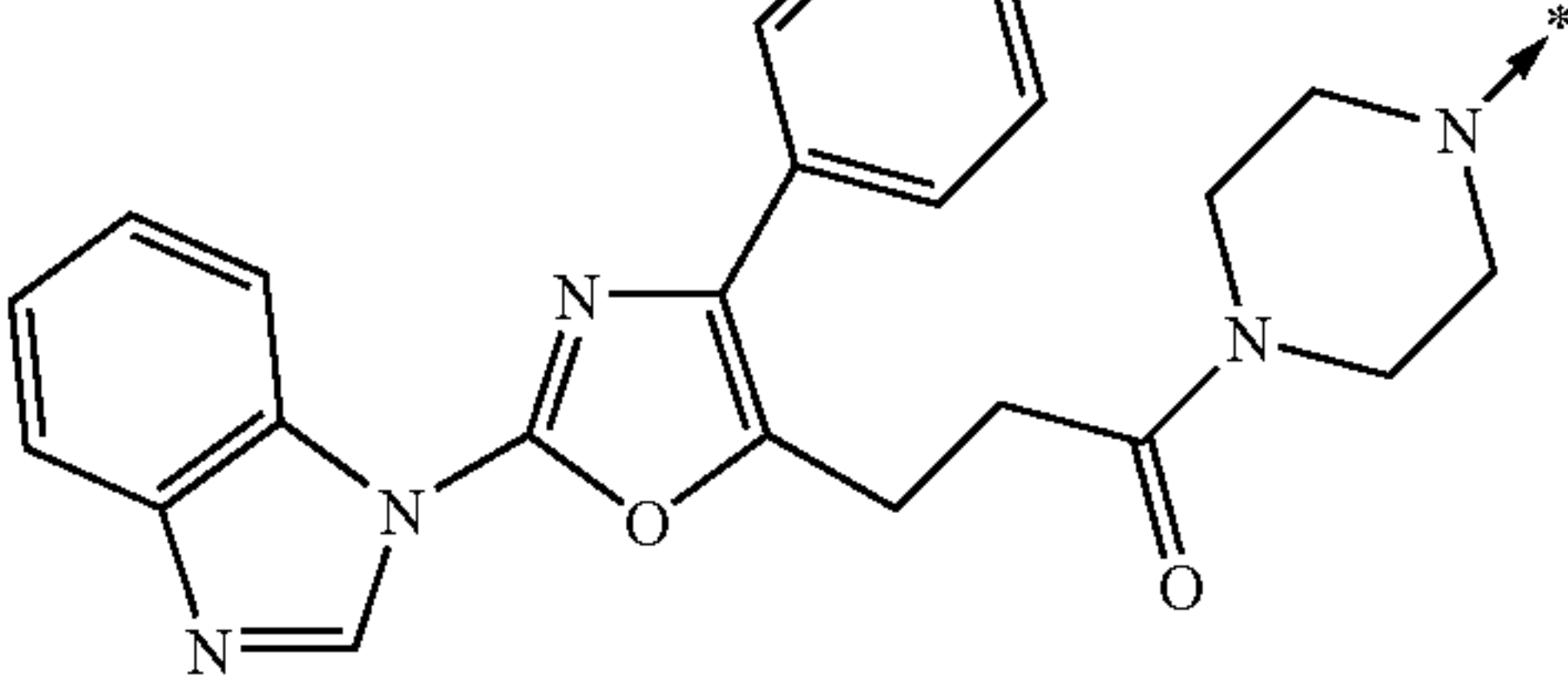
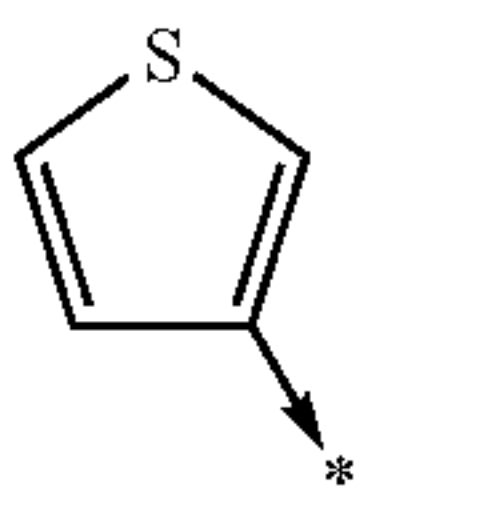
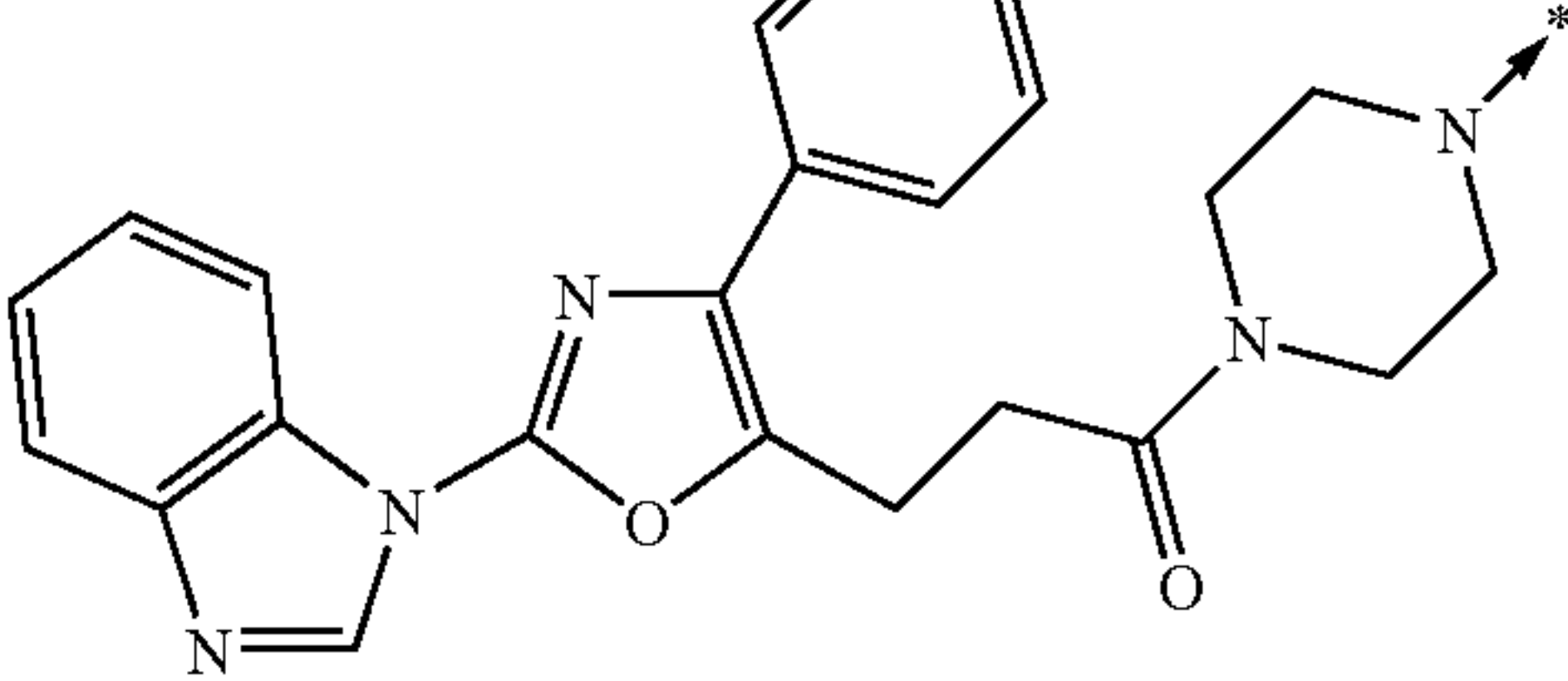
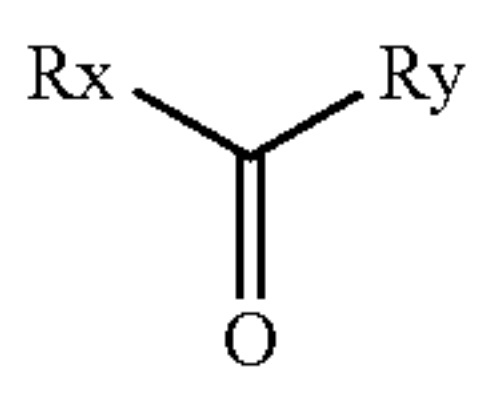
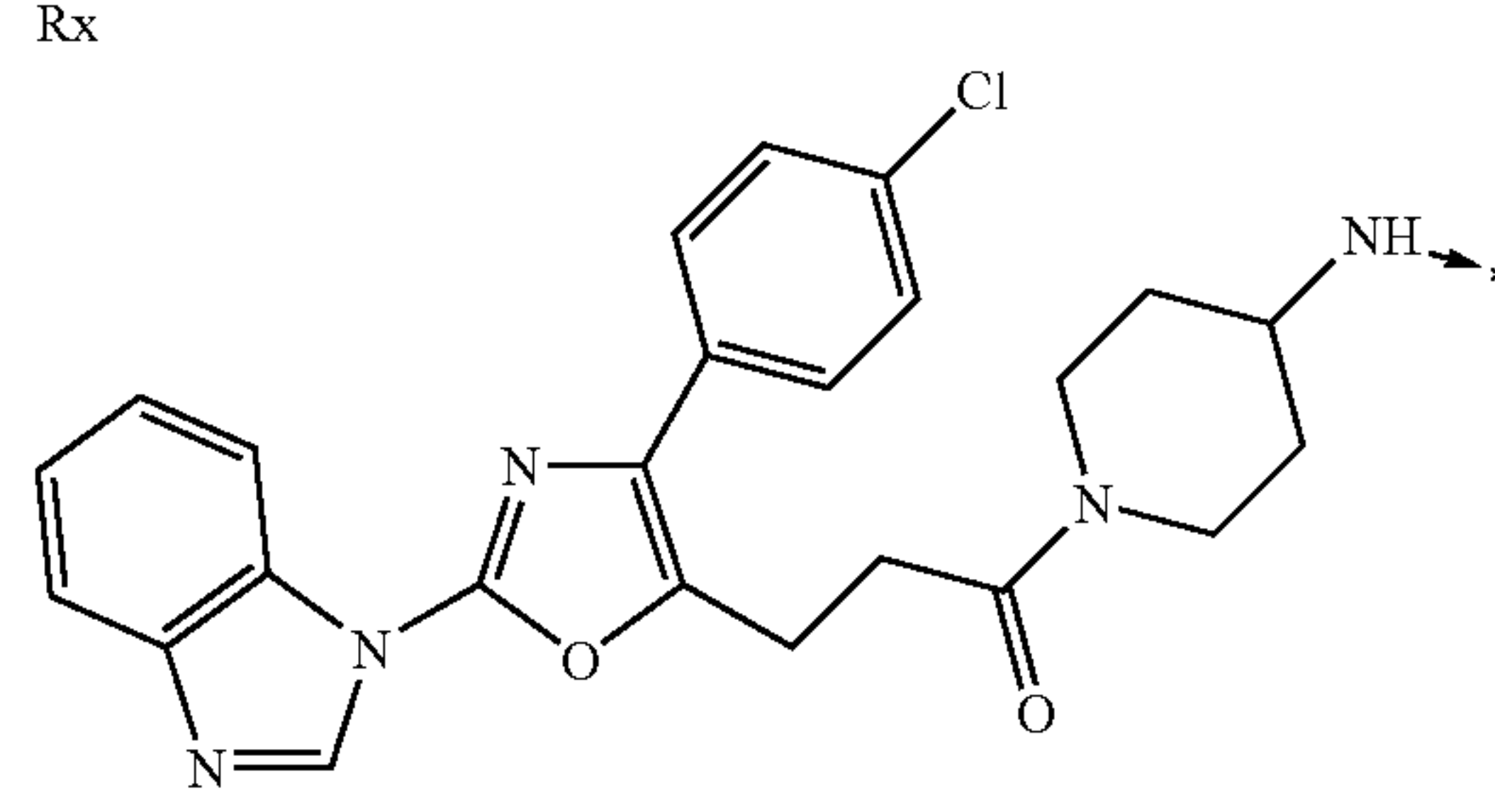
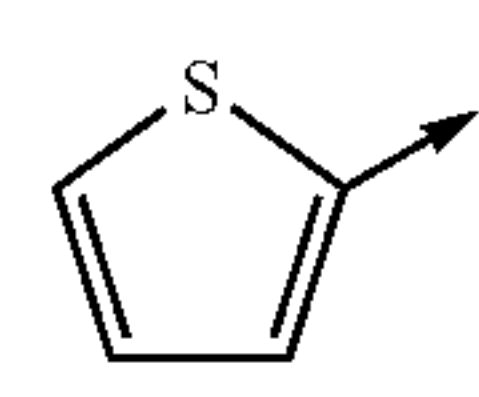
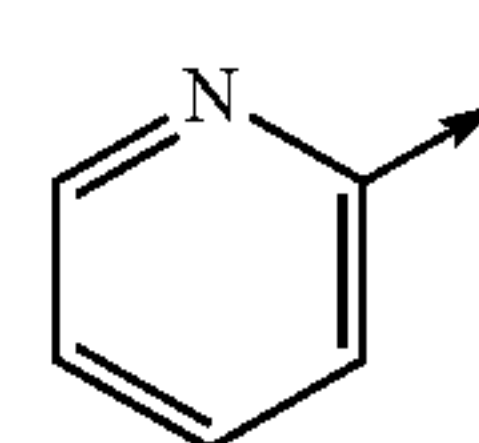
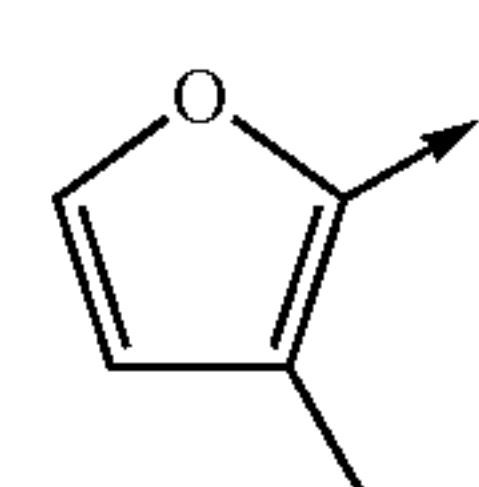
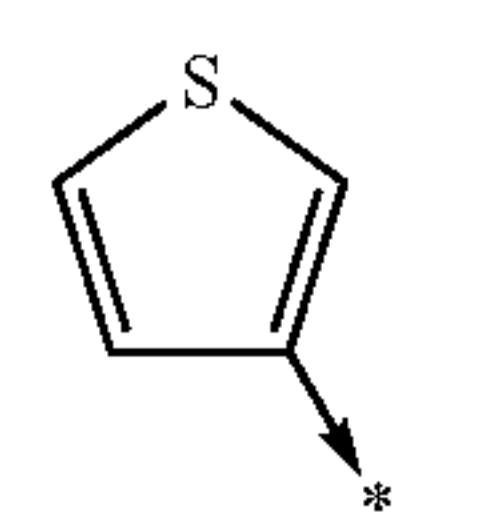
basic structure			
			
Rx	Ry		
			
	Example 372 20.1 mg, 99% 546 (M + 1)		Example 373 22.9 mg, 98% 546 (M + 1)
	Example 377 23.6 mg, 94% 541 (M + 1)		Example 378 28.1 mg, 97% 541 (M + 1)
	Example 383 23 mg, 99% 544 (M + 1)		Example 384 22.6 mg, 98% 544 (M + 1)
	Example 389 21.6 mg, 92% 546 (M + 1)		Example 390 20 mg, 99% 546 (M + 1)

TABLE 1-3-continued

basic structure	
	
Ry	Rx
	
	Example 374 18.2 mg, 98% 560 (M + 1)
	Example 379 18.4 mg, 98% 555 (M + 1)
	Example 385 19.6 mg, 98% 558 (M + 1)
	Example 391 16.9 mg, 97% 560 (M + 1)

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 1-4

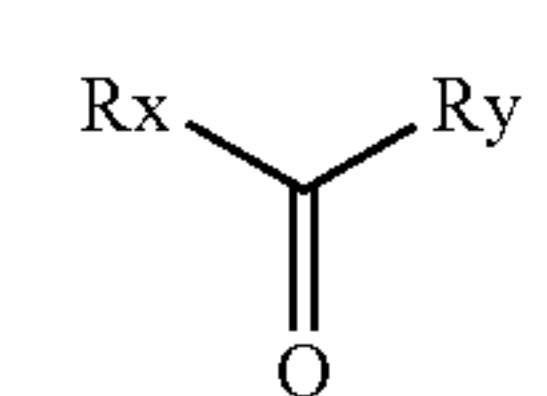
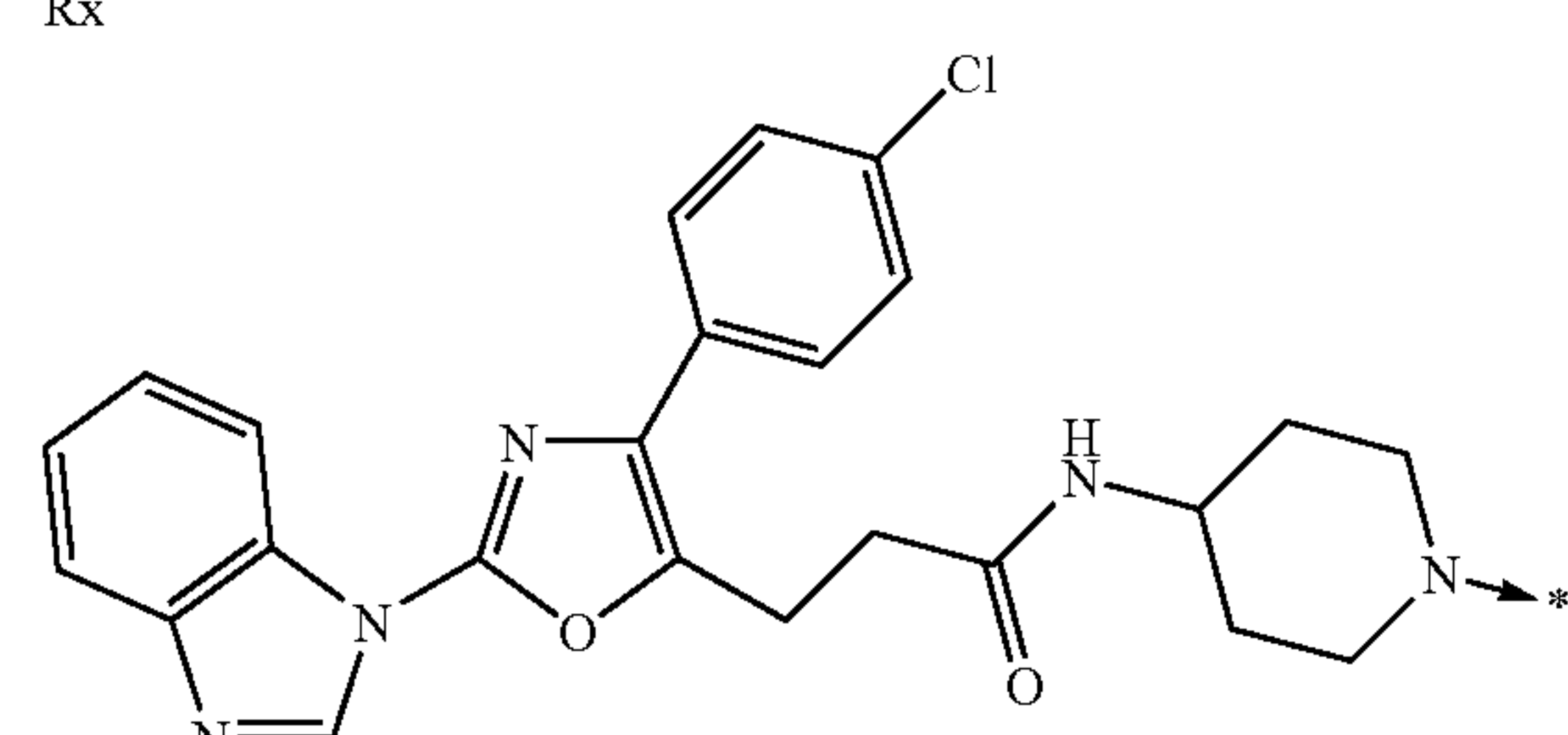
basic structure	
	
Ry	Rx
	

TABLE 1-4-continued

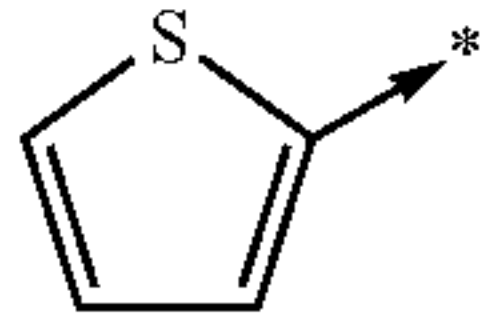
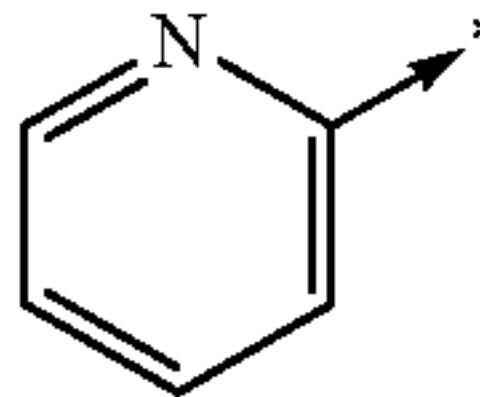
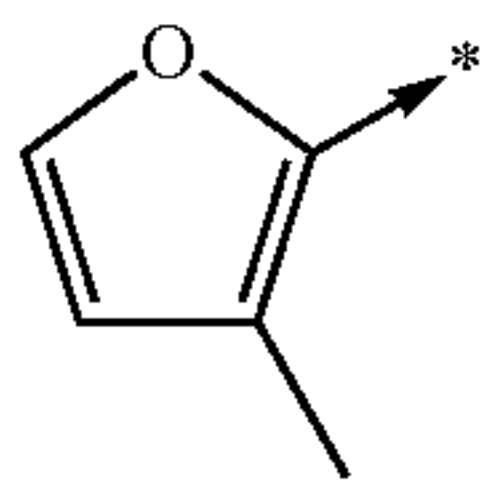
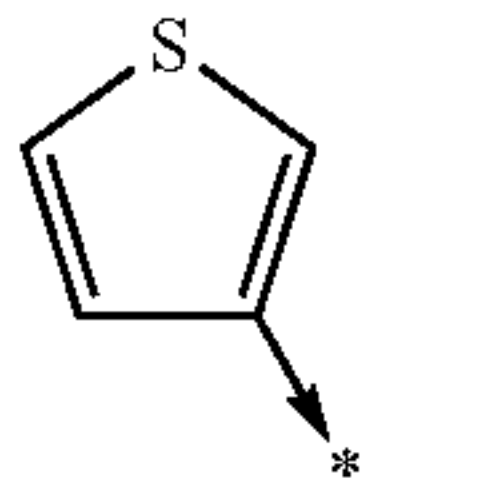
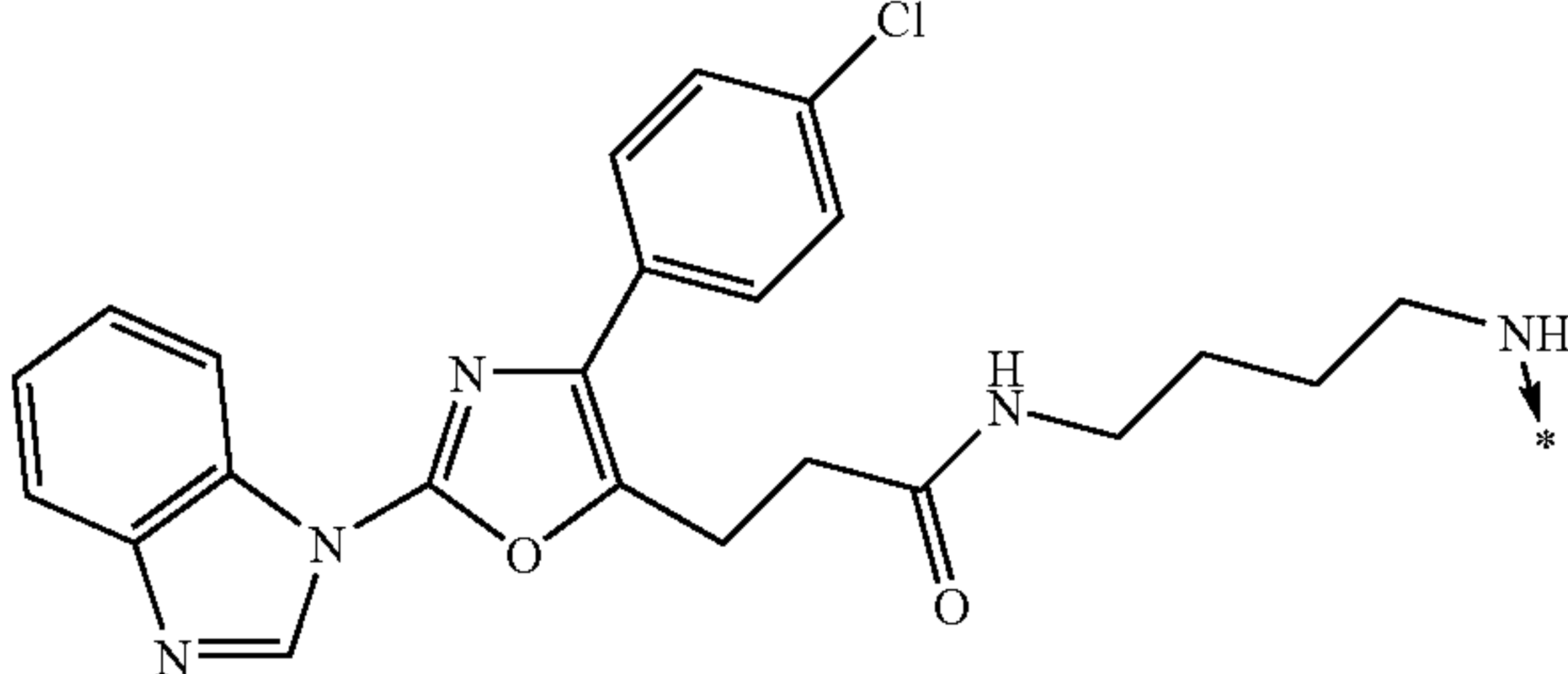
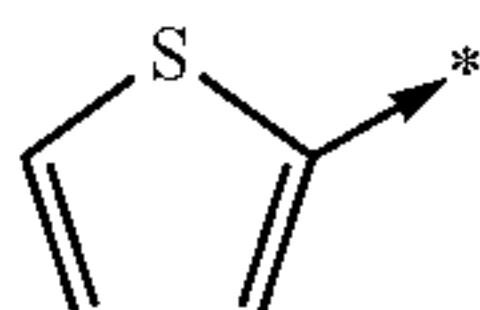
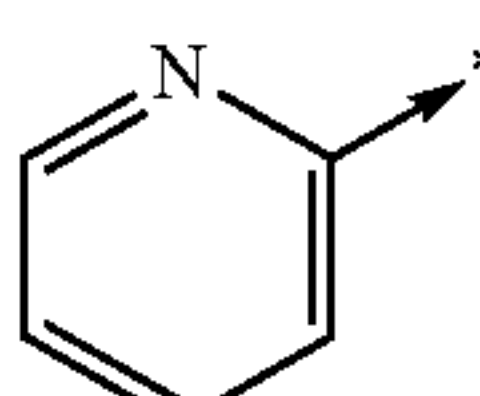
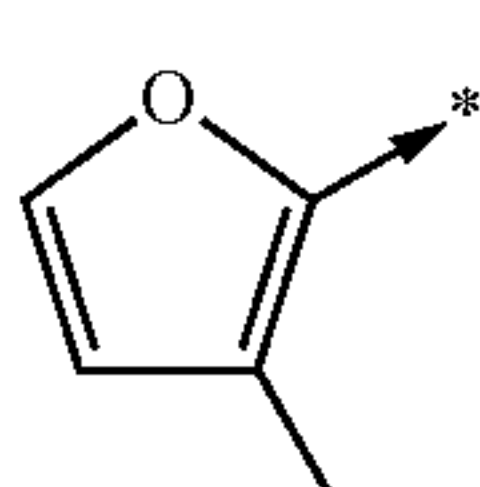
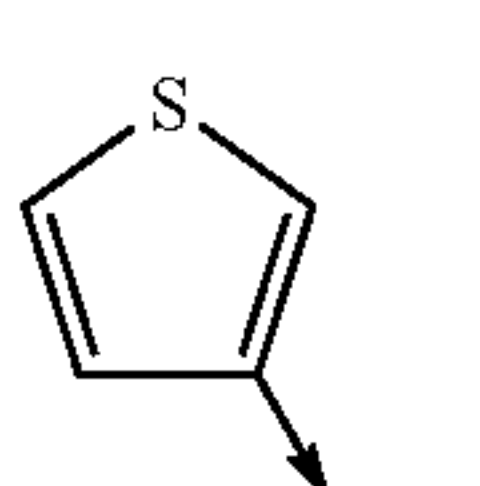
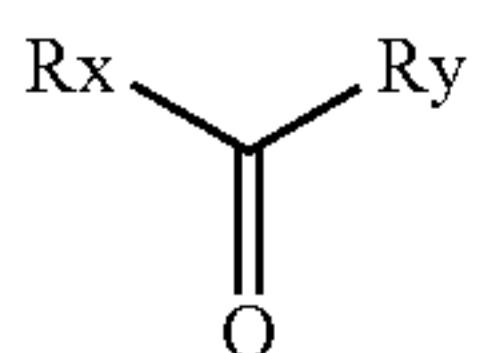
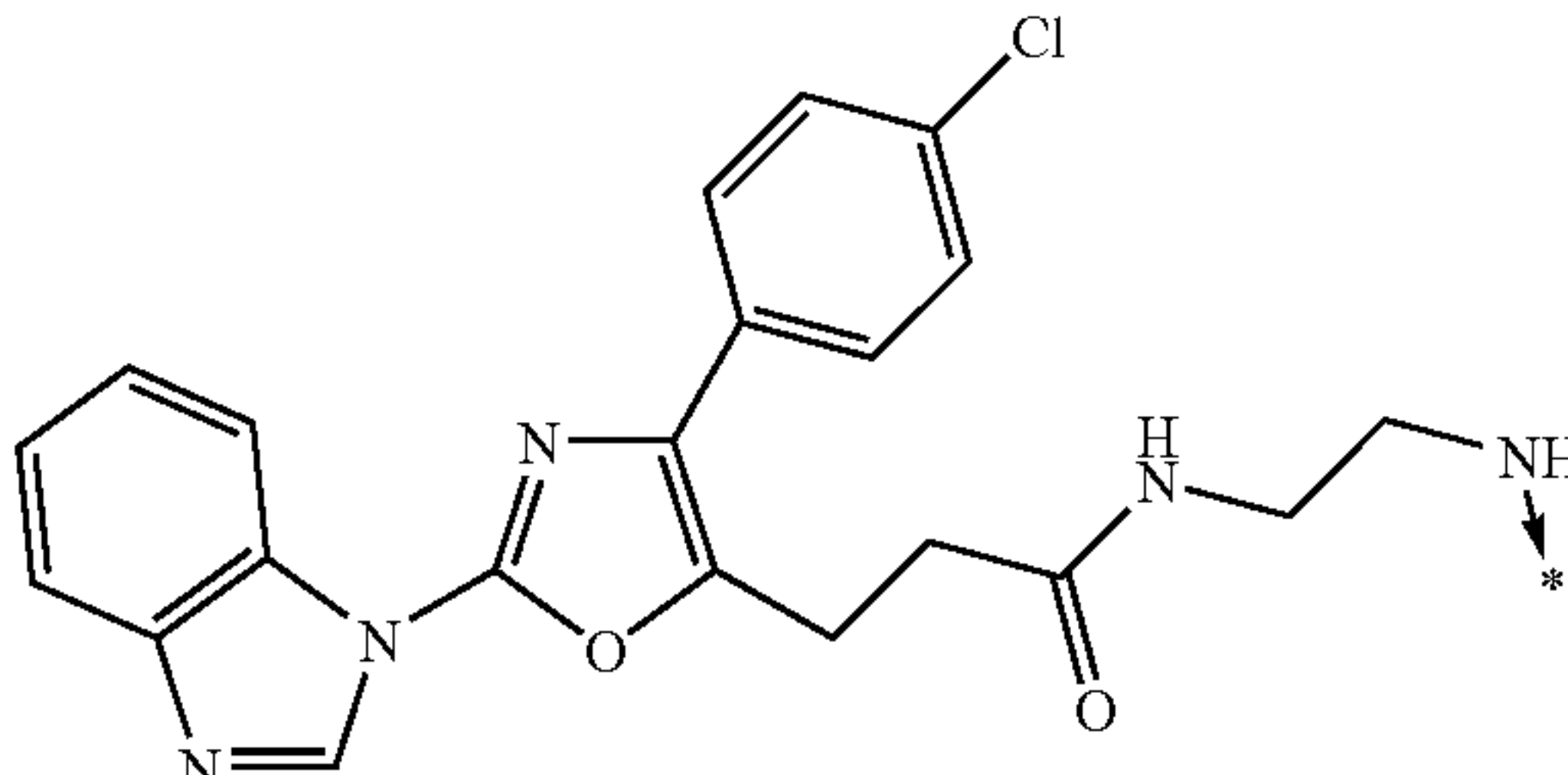
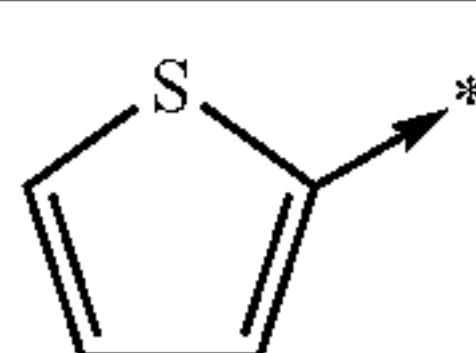
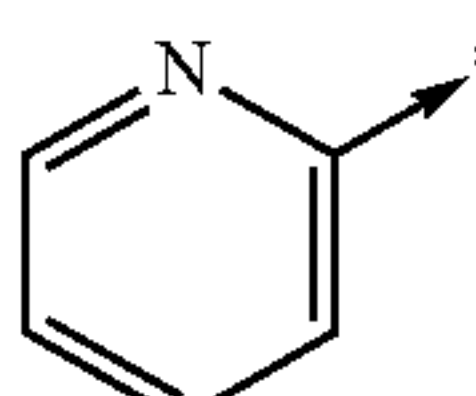
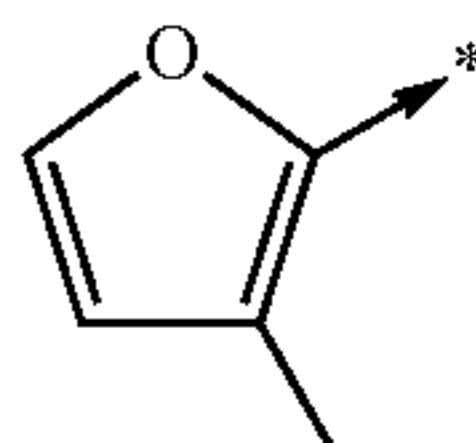
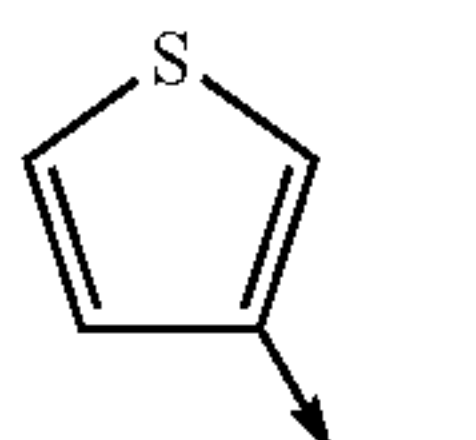
basic structure	
	$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$
	
	<p>Example 380 4.4 mg, 90% 555 (M + 1)</p>
	<p>Example 386 15.6 mg, 95% 558 (M + 1)</p>
	<p>Example 392 13.7 mg, 95% 560 (M + 1)</p>
Ry	Rx
	
	<p>Example 375 16.9 mg, 94% 548 (M + 1)</p>
	<p>Example 381 17.9 mg, 97% 543 (M + 1)</p>
	<p>Example 387 20.2 mg, 546 (M + 1)</p>
	<p>Example 393 15.9 mg, 98% 548 (M + 1)</p>

TABLE 1-4-continued

basic structure	
	
Ry	Rx
	
	<p>Example 376 26.3 mg, 98% 520 (M + 1)</p>
	<p>Example 382 15.6 mg, 85% 515 (M + 1)</p>
	<p>Example 388 18.1 mg, 95% 518 (M + 1)</p>
	<p>Example 394 19.4 mg, 85% 520 (M + 1)</p>

upper line: Example No.
middle line: yield, LC-MS purity (220 nm)
lower line: MS (ESI+, m/e)

Example 395

A mixture of 2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolepropionic acid (22 mg), 3-amino-1-Boc-pyrrolidine (12 mg), 1-hydroxy-7-azabenzotriazole (10 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (12 mg) and N,N-dimethylformamide (1 ml) was shaken at room temperature for 8 hrs. The reaction mixture was poured into 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was filtered and concentrated. The residue was dissolved in 4N hydrochloric acid ethyl acetate solution, left standing for 5 min. and concentrated. To the residue were added (2R)-tetrahydrofuran-2-carboxylic acid (12 mg), 1-hydroxybenzotriazole (20 mg), dicyclohexylcarbodiimide (13 mg), N,N-

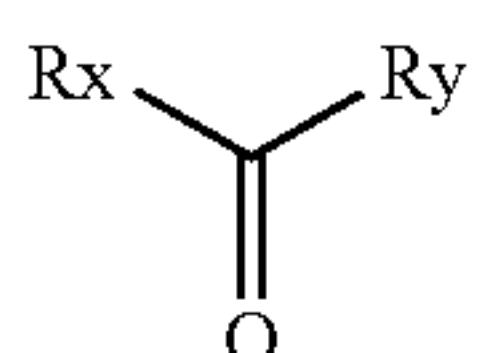
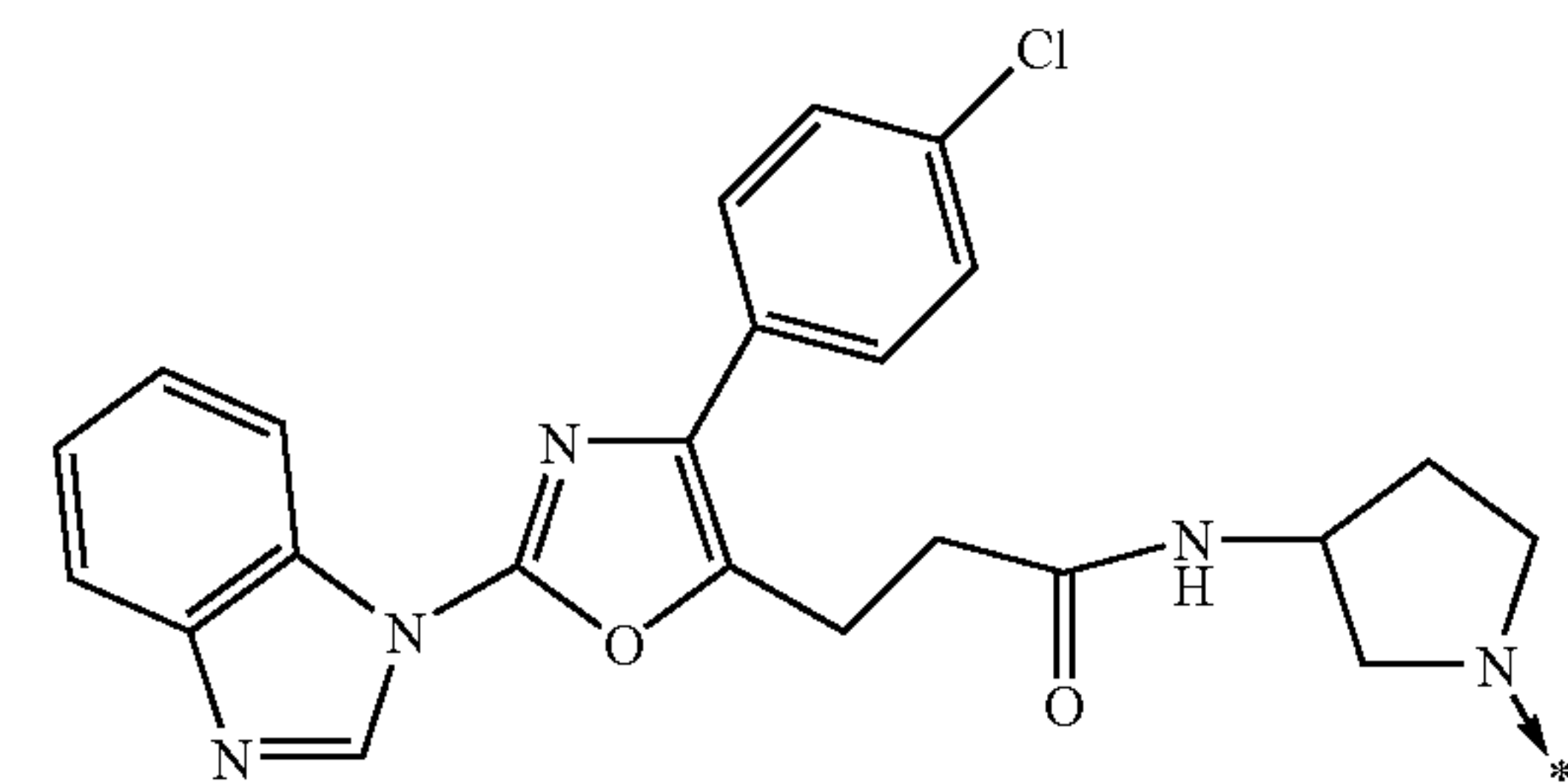
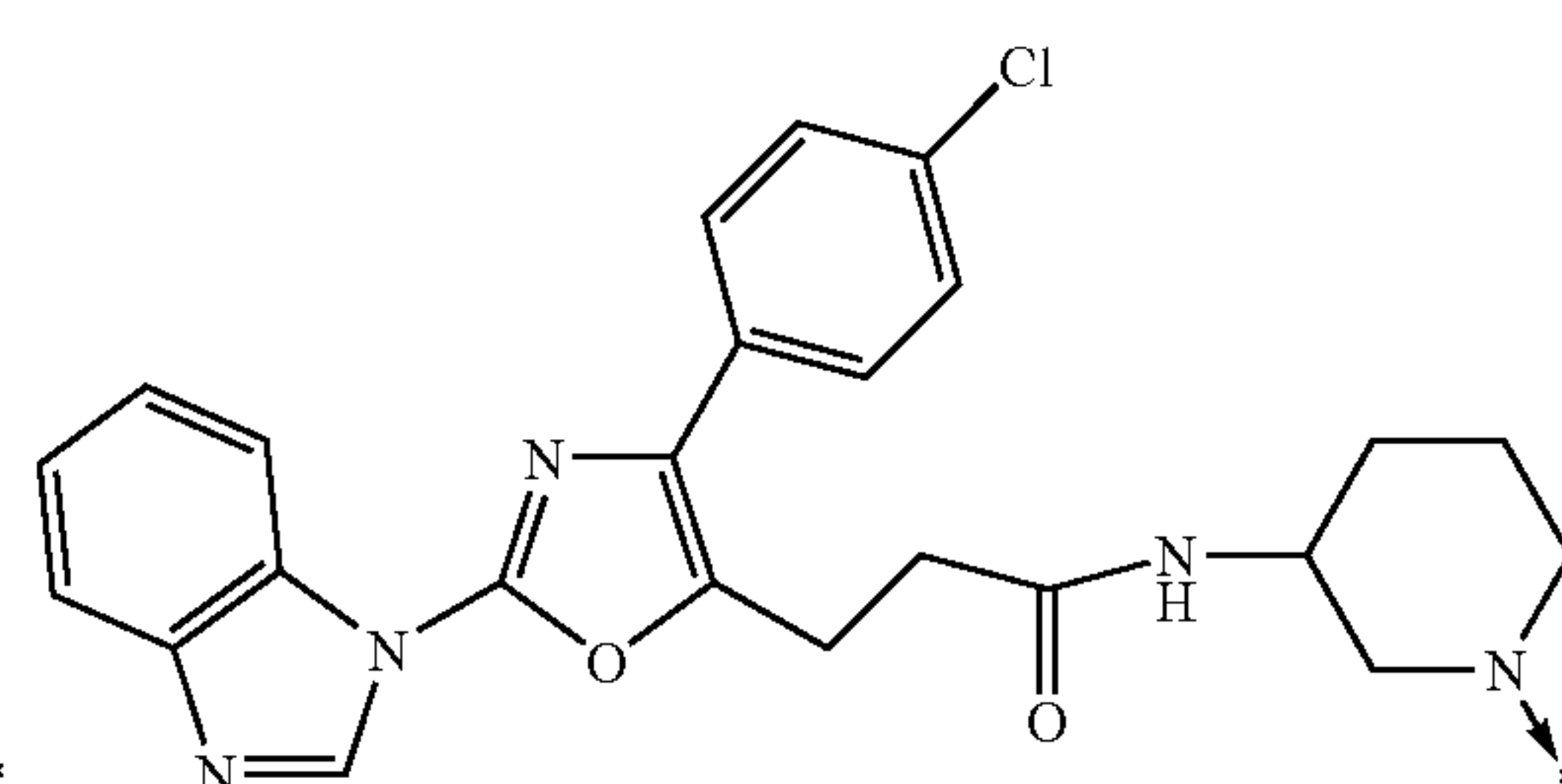
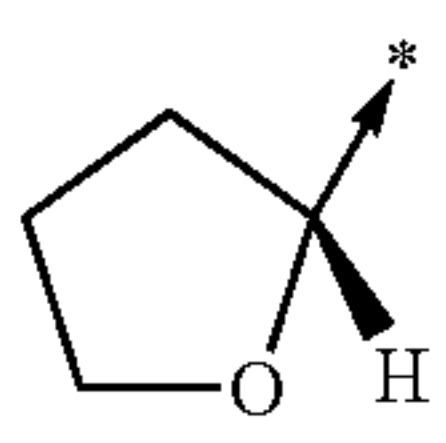
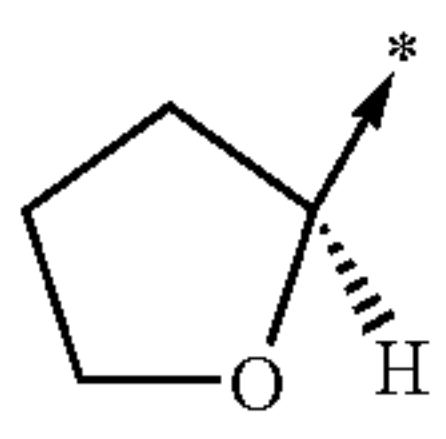
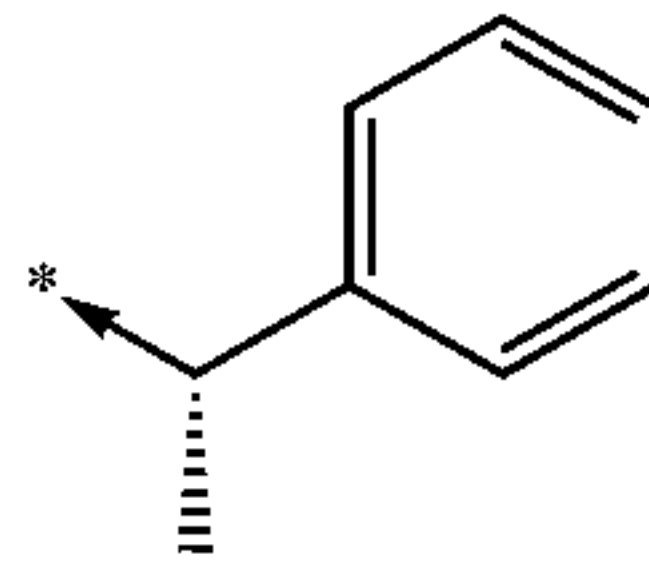
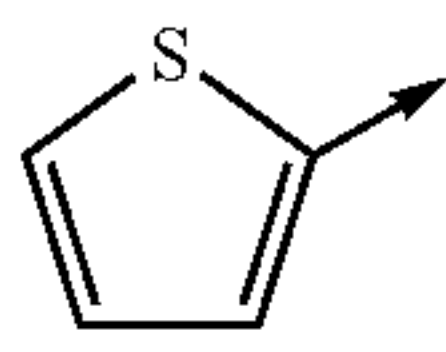
dimethylformamide (1 ml), and the mixture was shaken at room temperature for 16 hrs. The reaction mixture was poured into Mega Bond Elut SCX column (1 g) (manufactured by Varian Inc.) equilibrated in advance with acetonitrile and impurities were washed out with acetonitrile. The object compound was eluted with 2N ammonia methanol solution and concentrated.

Examples 396–454

In the same manner as in Example 395, the object compounds were obtained.

The structure and purity of the object compounds of Examples 395–454 were confirmed by LC-MS, HPLC. The yield, structure, purity and mass spectrum data of the object compounds are shown in [Table 2-1]–[Table 2-8].

TABLE 2-1

basic structure	
	
Rx	
Ry	
	
	<p>Example 395 19.2 mg, 96% 534 (M + 1)</p>
	<p>Example 396 18.2 mg, 91% 548 (M + 1)</p>
	<p>Example 399 15.1 mg, 98% 548 (M + 1)</p>
	<p>Example 402 13.3 mg, 80% 568 (M + 1)</p>
	<p>Example 403 13.5 mg, 83% 582 (M + 1)</p>
	<p>Example 405 12.7 mg, 90% 546 (M + 1)</p>
	<p>Example 406 11.1 mg, 91% 560 (M + 1)</p>

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 2-2

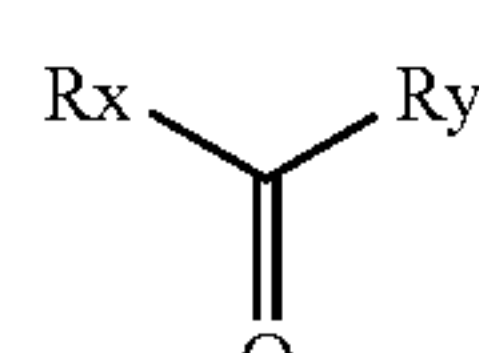
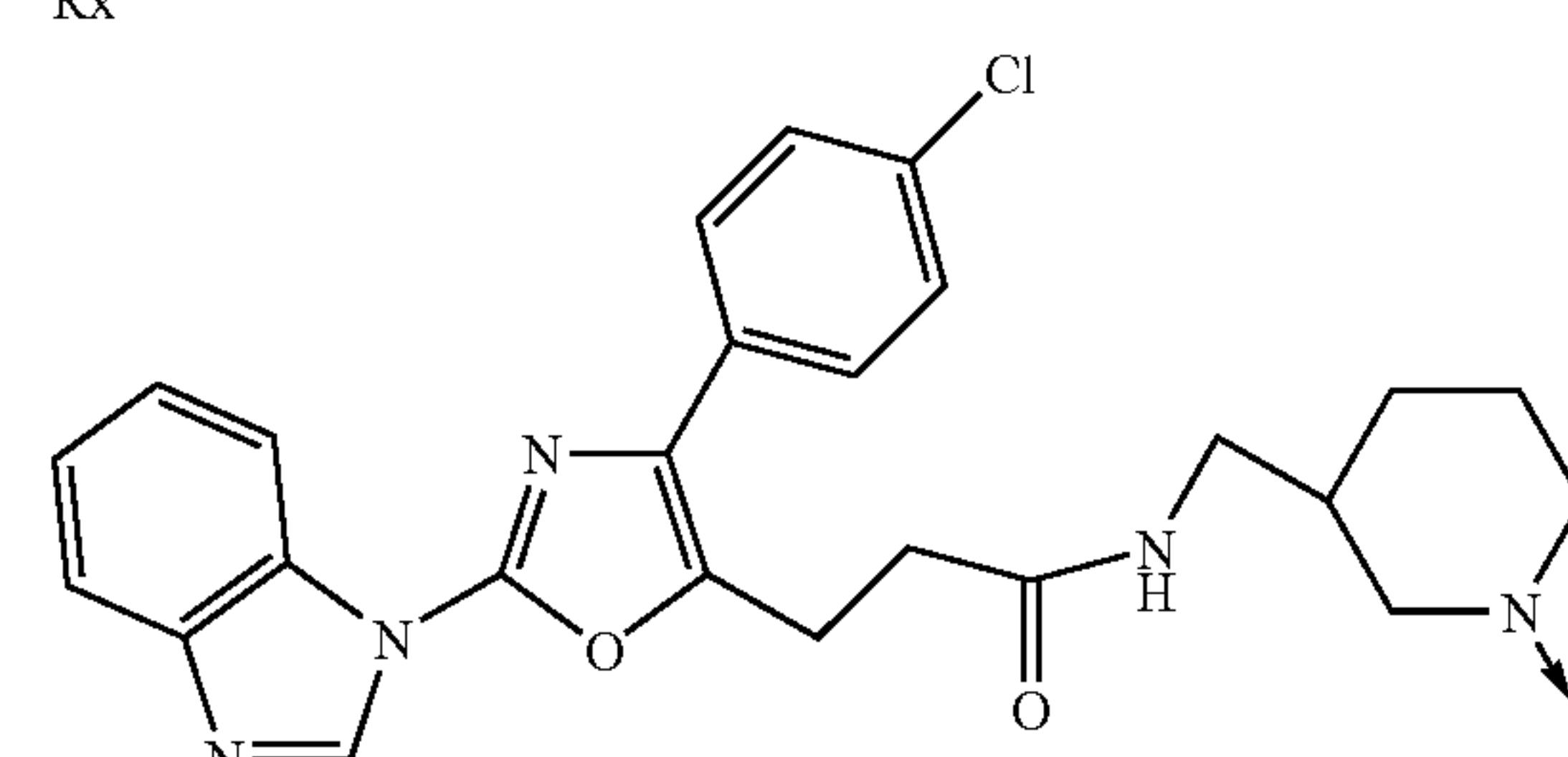
basic structure	
	
Rx	
Ry	

TABLE 2-2-continued

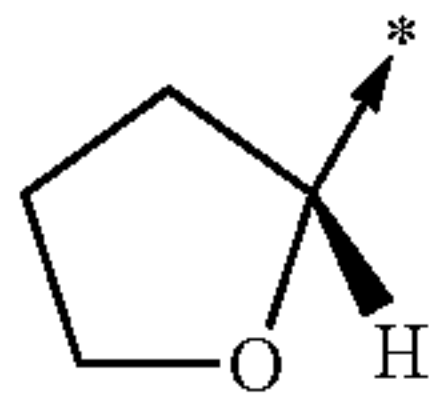
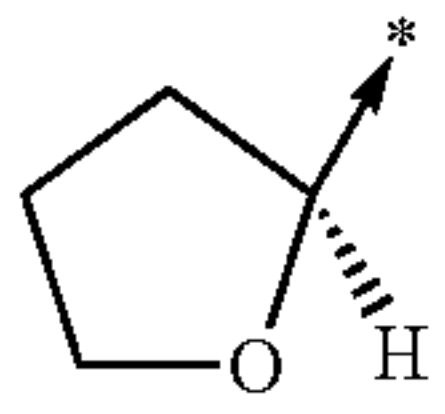
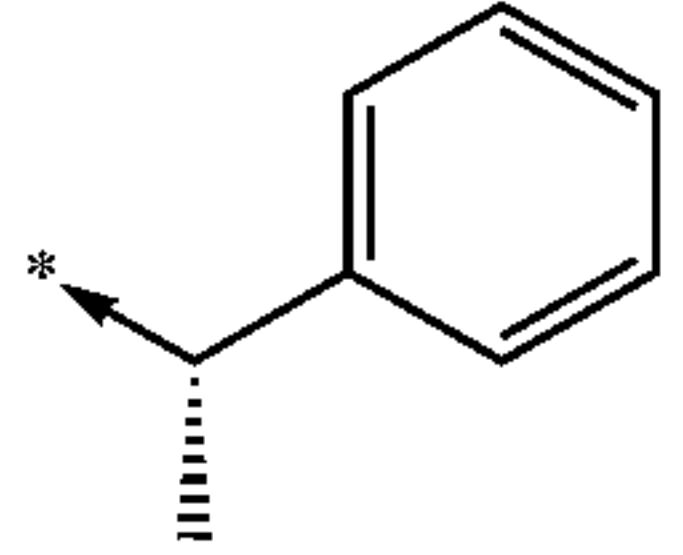
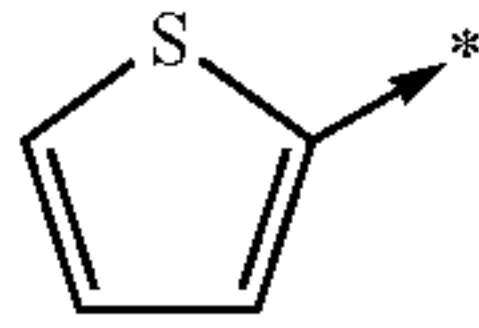
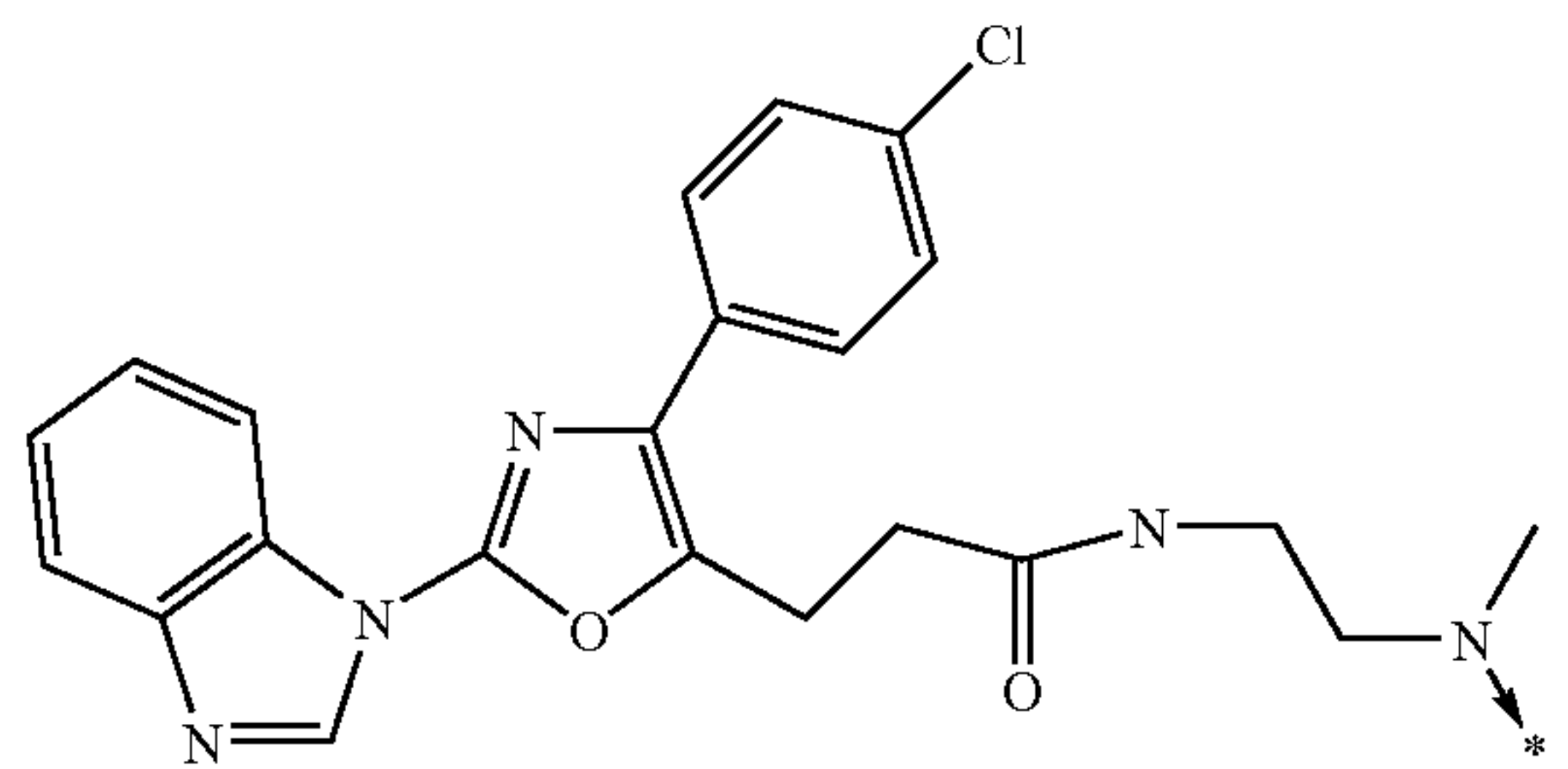
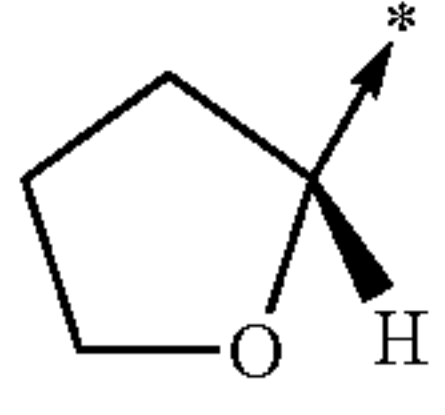
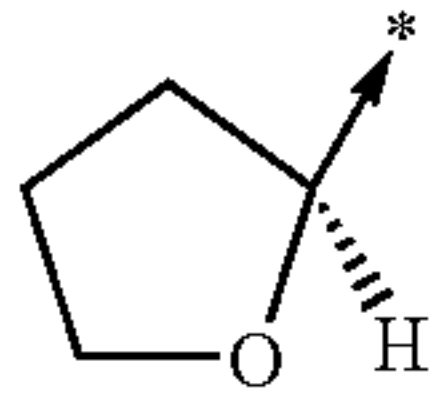
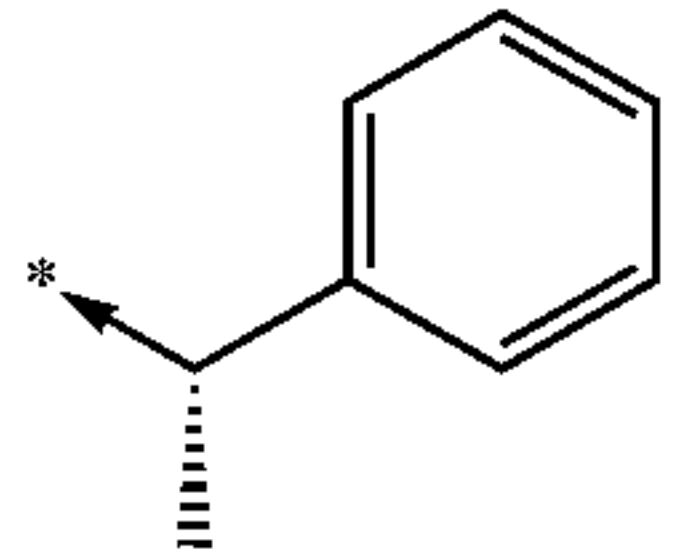
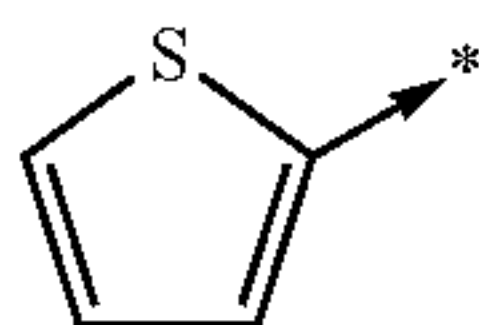
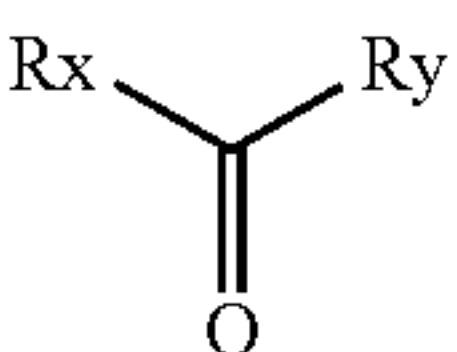
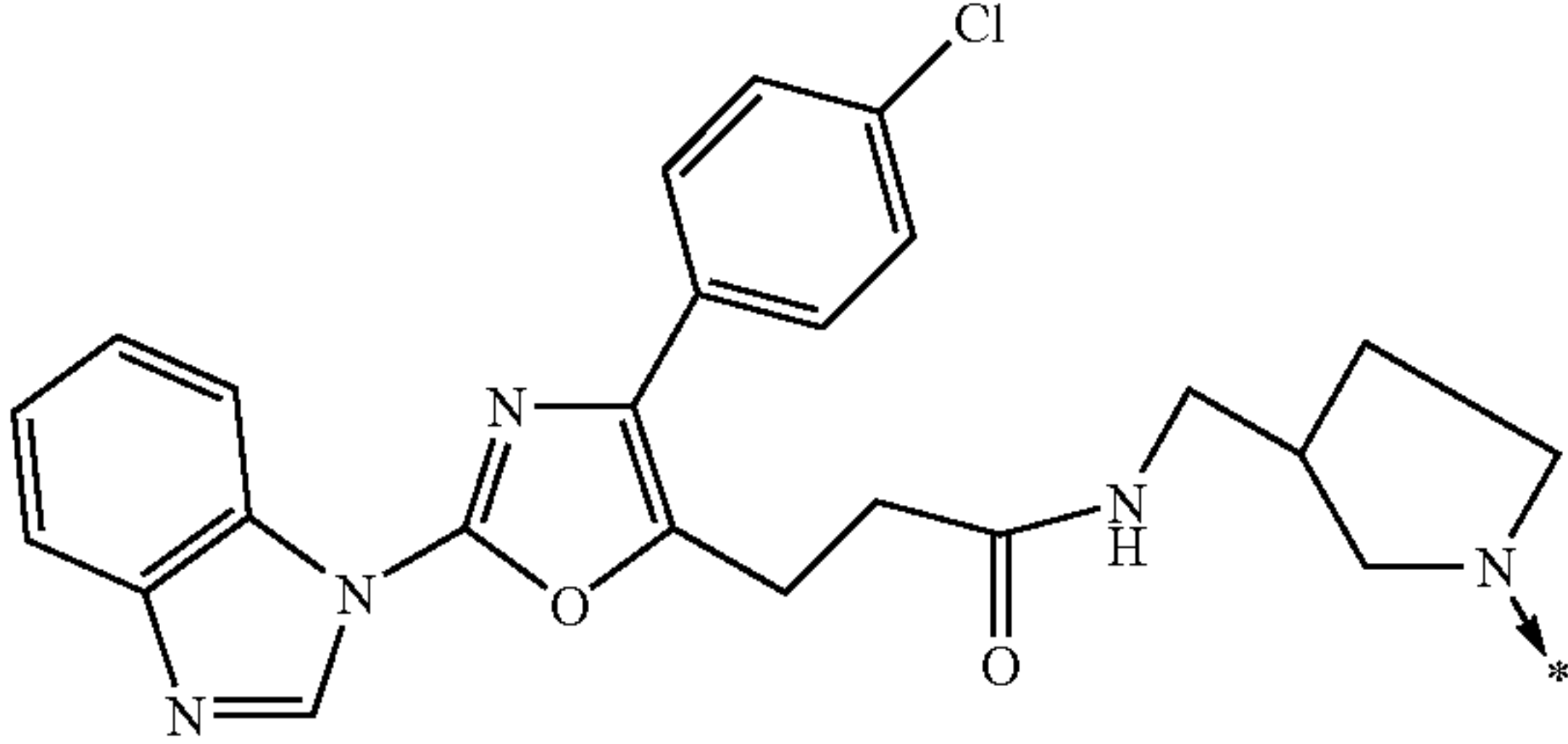
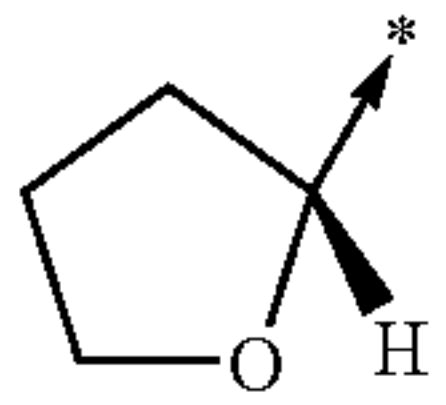
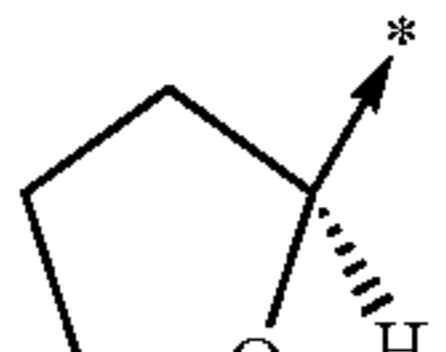
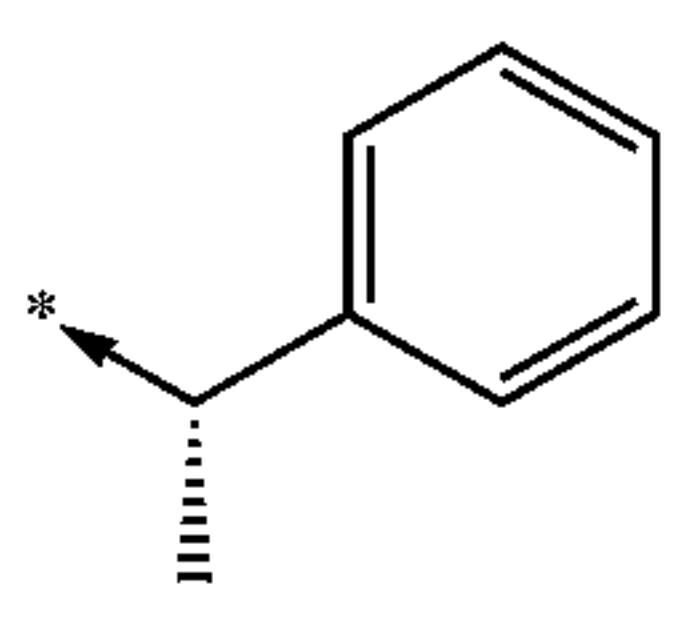
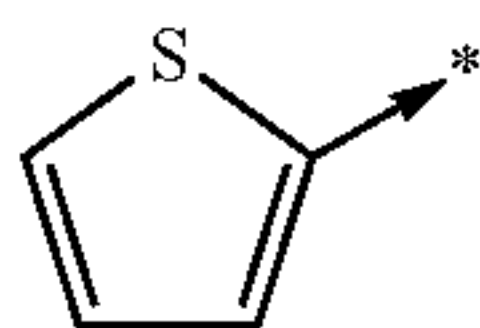
basic structure	
	$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$
	Example 397 23.2 mg, 85% 562 (M + 1)
	Example 400 19.9 mg, 87% 562 (M + 1)
	
	Example 407 15.2 mg, 91% 574 (M + 1)
Ry	Rx
	
	Example 398 23.3 mg, 91% 522 (M + 1)
	Example 401 21.3 mg, 94% 522 (M + 1)
	Example 404 20.8 mg, 80% 556 (M + 1)
	Example 408 18.1 mg, 80% 534 (M + 1)

TABLE 2-2-continued

basic structure	
Ry	Rx
	
	
	
	
	
	
	Example 409 10.2 mg, 94% 560 (M + 1)

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 2-3

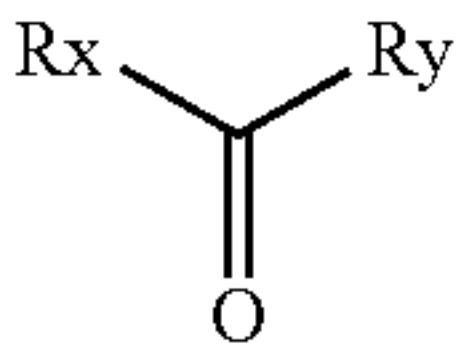
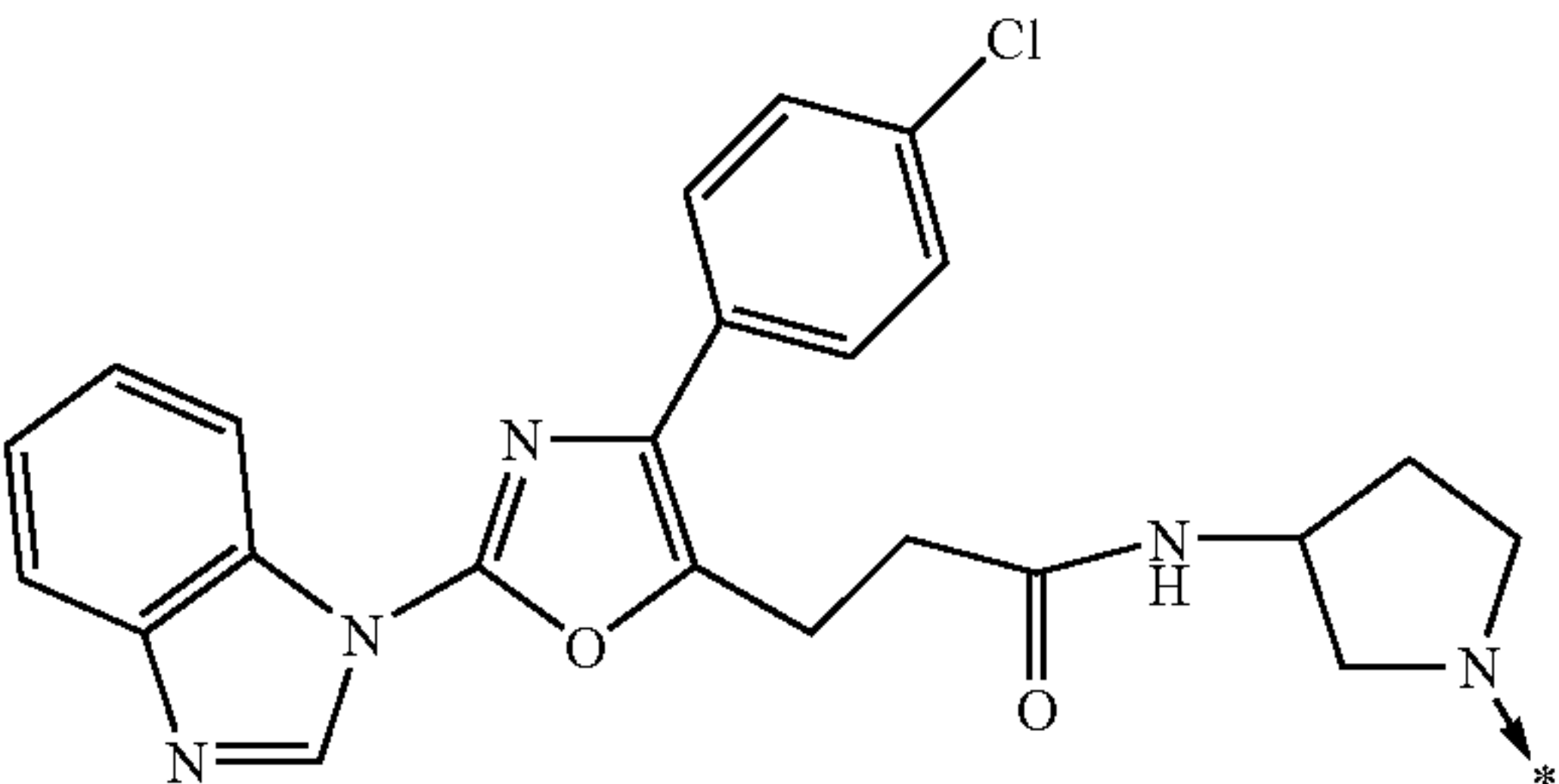
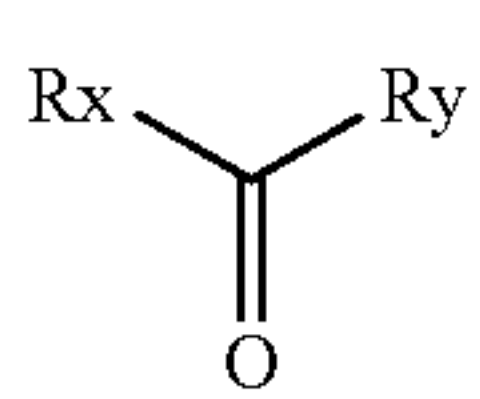
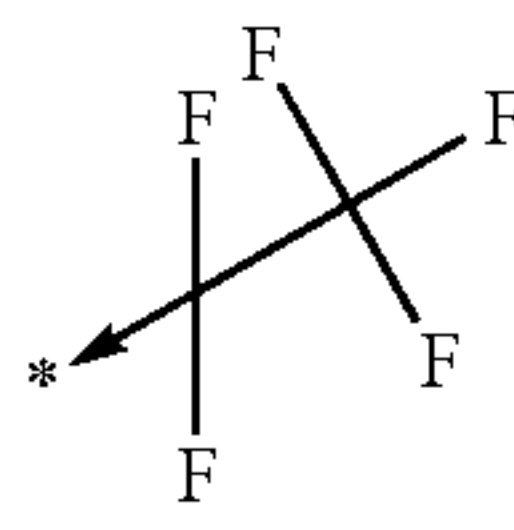
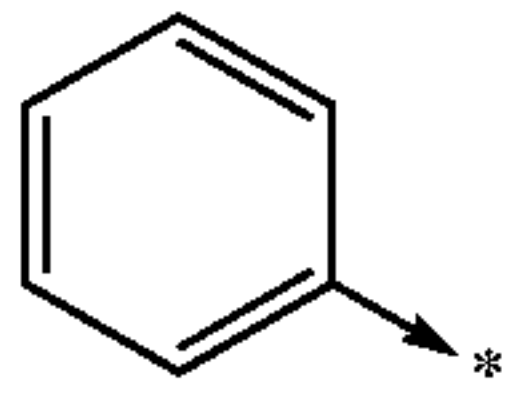
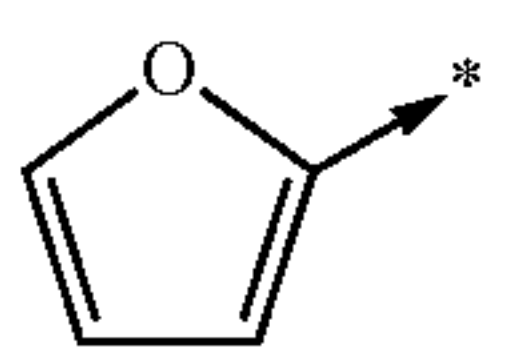
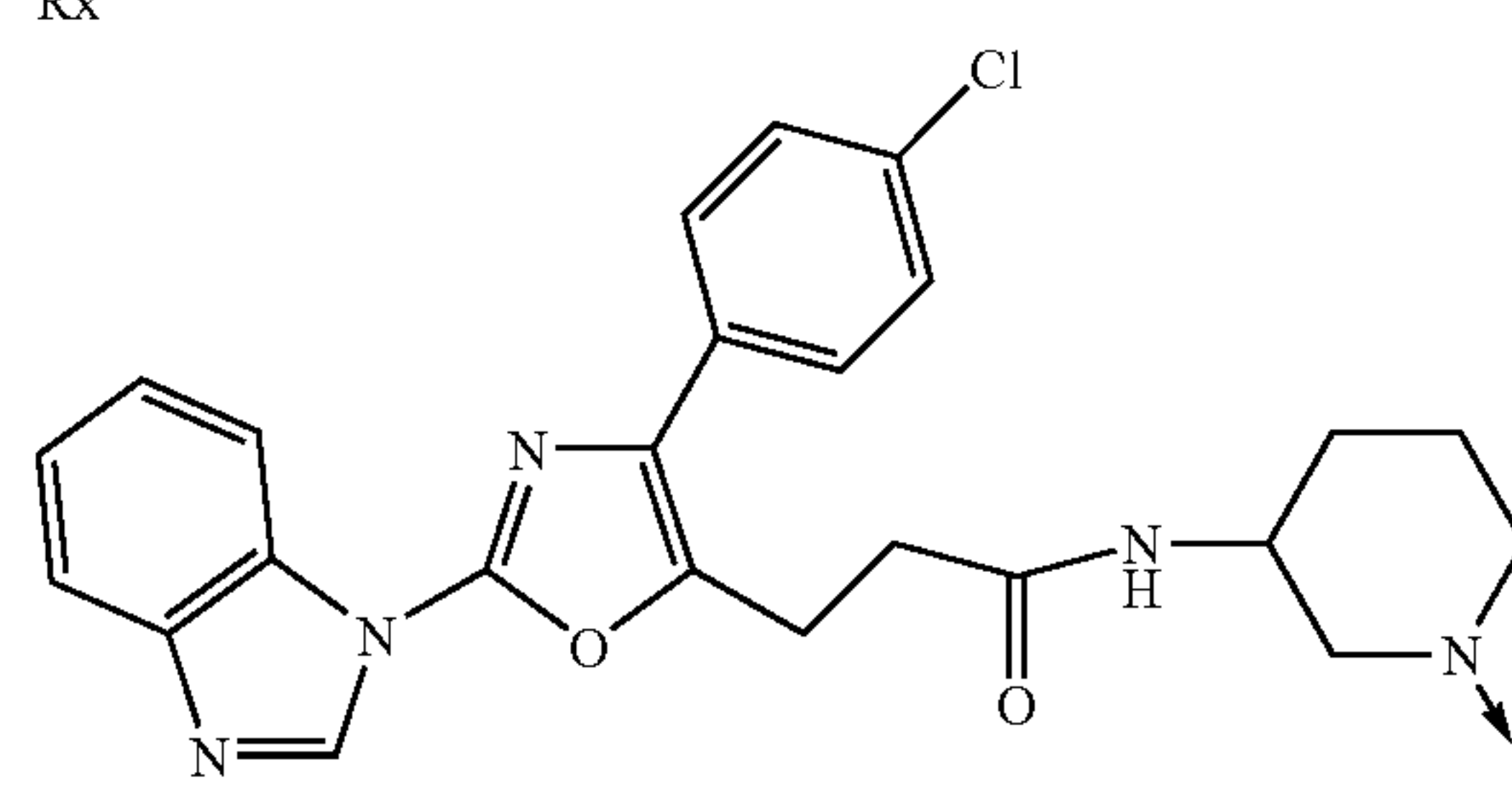
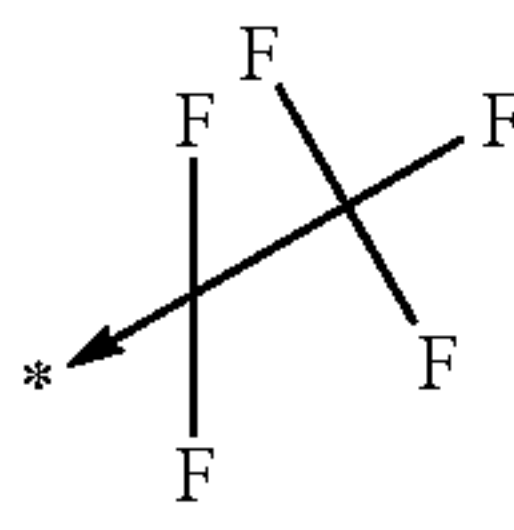
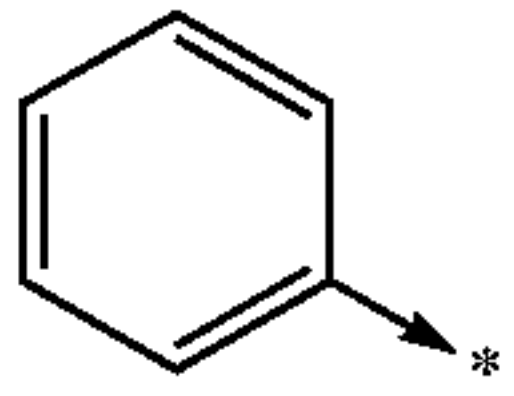
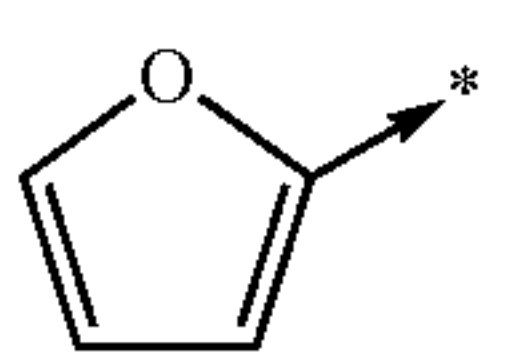
basic structure	
Ry	Rx
	
	

TABLE 2-3-continued

basic structure	
	
	<p>Example 410 9.3 mg, 81% 582 (M + 1)</p>
	<p>Example 416 17.8 mg, 92% 540 (M + 1)</p>
	<p>Example 421 17.6 mg, 90% 530 (M + 1)</p>
Ry	Rx
	
	<p>Example 412 8 mg, 83% 596 (M + 1)</p>
	<p>Example 417 15.9 mg, 92% 554 (M + 1)</p>
	<p>Example 422 34.2 mg, 94% 544 (M + 1)</p>

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 2-4

basic structure		
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ / \\ \text{O} \end{array}$		
	Rx	
Ry		
	<p>Example 413 14.7 mg, 80% 610 (M + 1)</p>	<p>Example 414 4 mg, 90% 570 (M + 1)</p>
	<p>Example 418 22 mg, 93% 568 (M + 1)</p>	<p>Example 419 22 mg, 83% 528 (M + 1)</p>
	<p>Example 423 24 mg, 91% 558 (M + 1)</p>	<p>Example 424 32 mg, 94% 518 (M + 1)</p>
	Ry	Rx
		<p>Example 415 4.7 mg, 80% 596 (M + 1)</p>
		<p>Example 420 10.9 mg, 85% 554 (M + 1)</p>
		<p>Example 425 17.5 mg, 87% 544 (M + 1)</p>

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 2-5

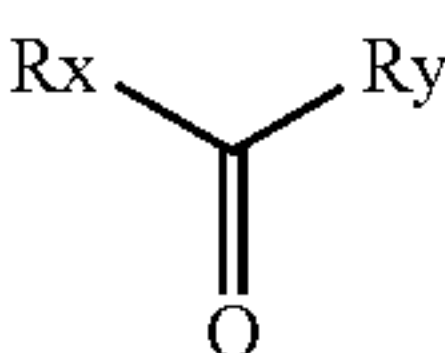
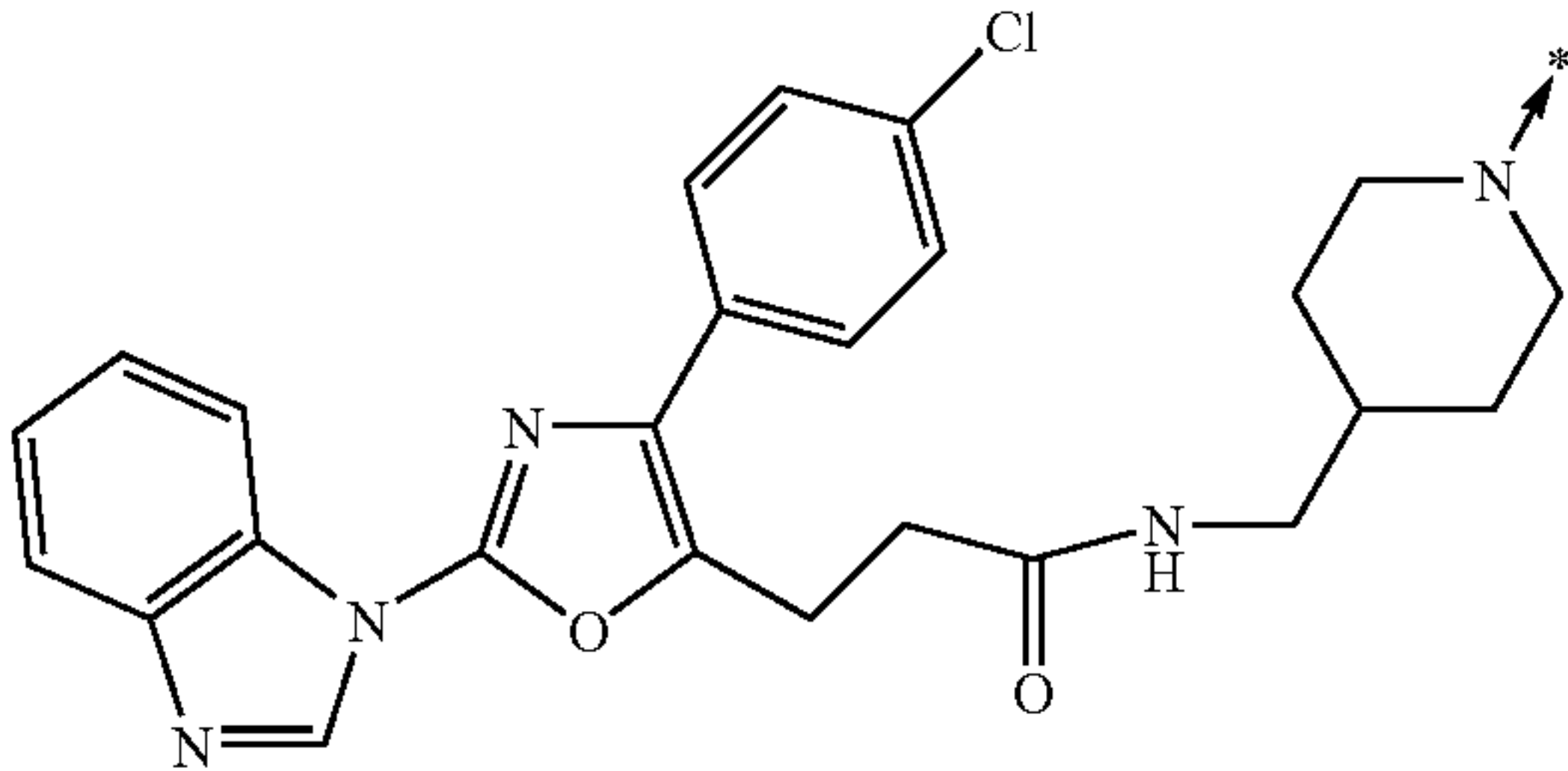
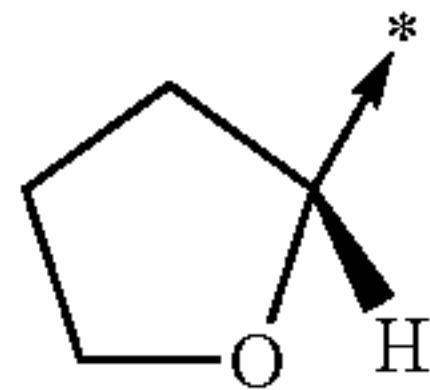
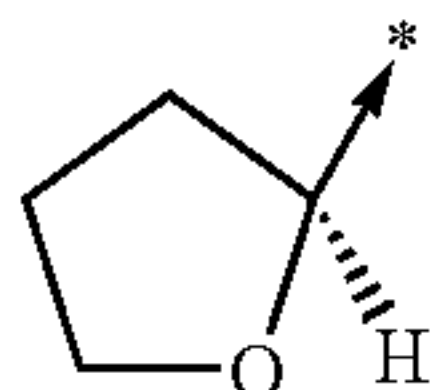
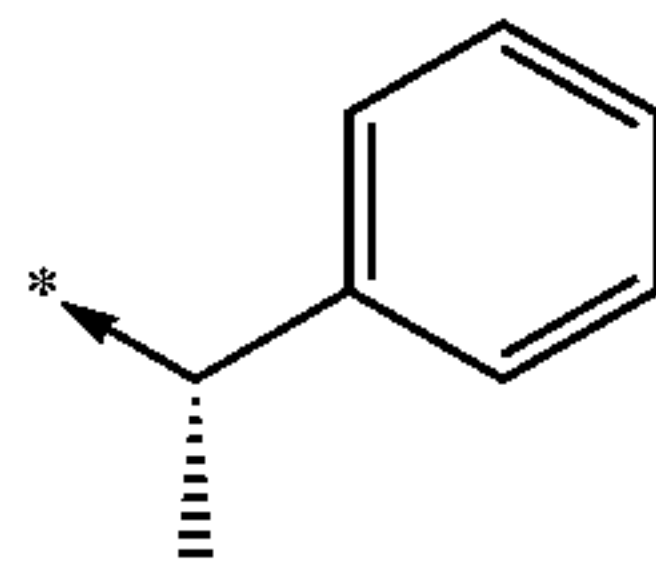
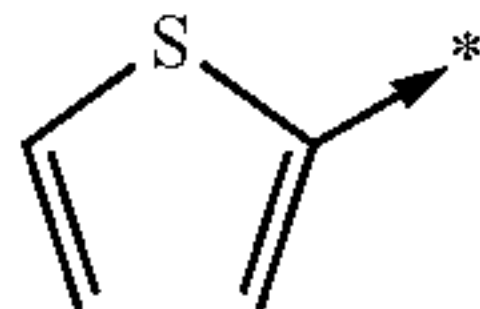
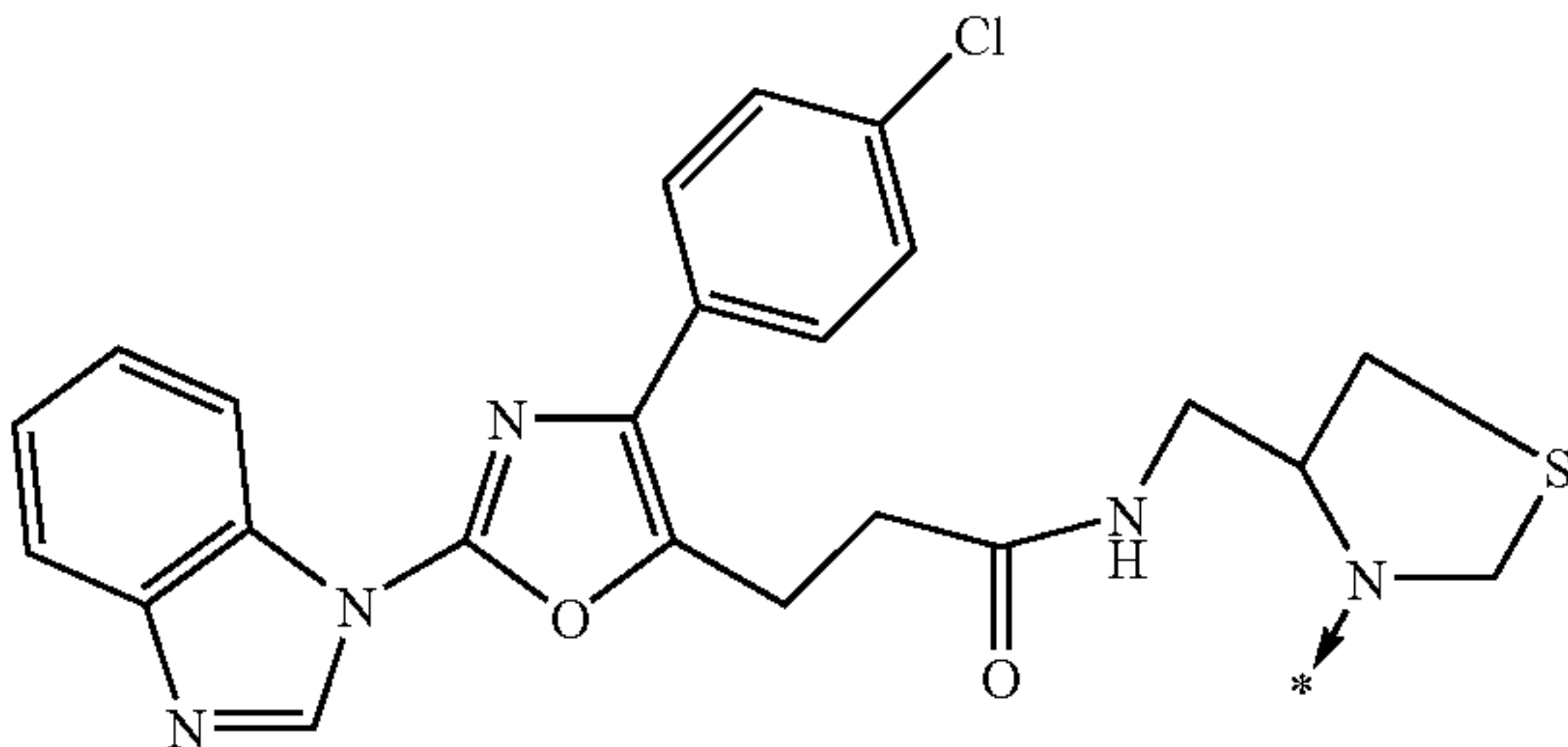
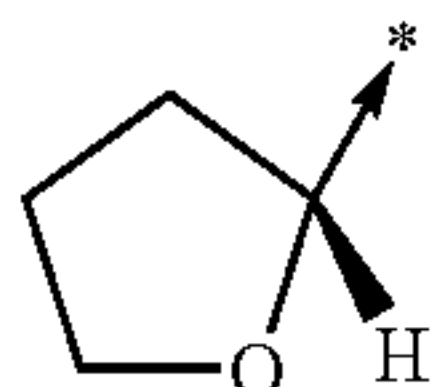
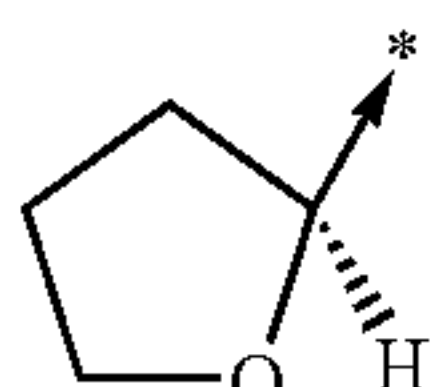
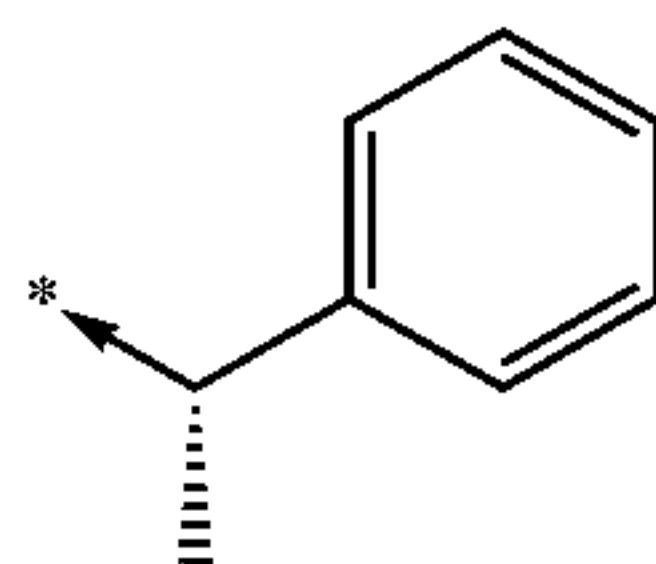
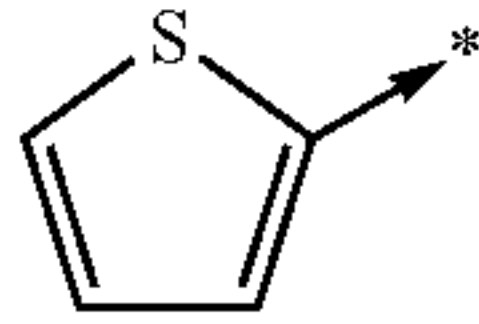
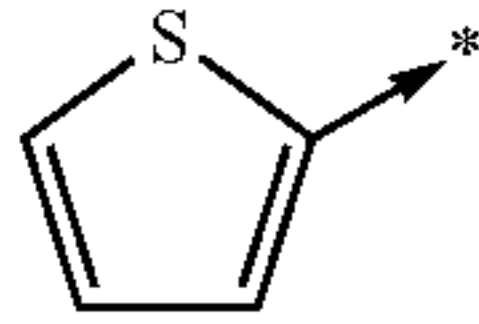
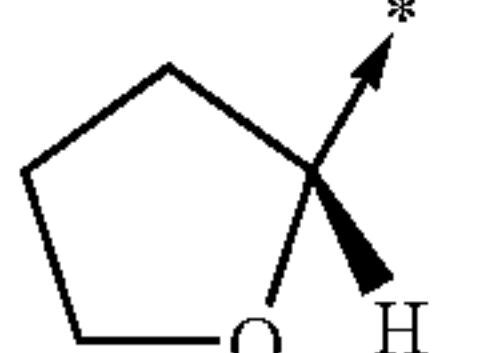
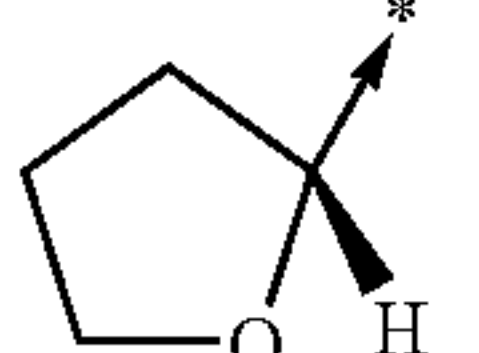
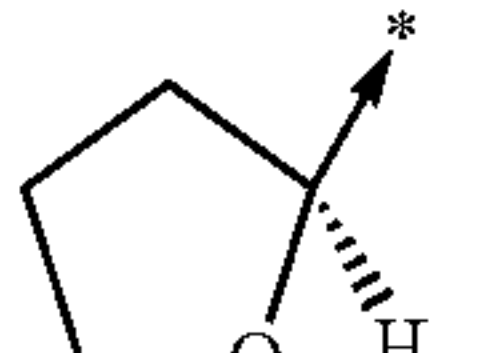
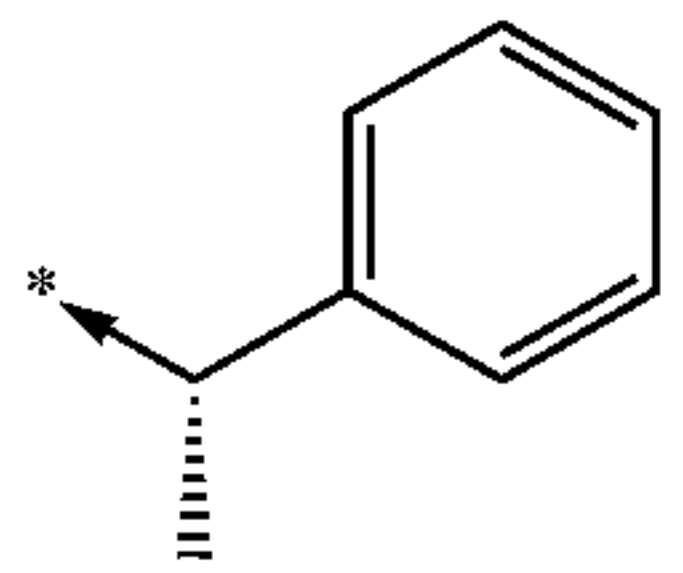
basic structure	
Ry	Rx
	
Ry	Rx
	
	<p>Example 426 21.4 mg, 93% 562 (M + 1)</p>
	<p>Example 432 19.8 mg, 96% 562 (M + 1)</p>
	<p>Example 437 19.5 mg, 80% 596 (M + 1)</p>
	<p>Example 443 22.3 mg, 95% 574 (M + 1)</p>
Ry	Rx
	
	<p>Example 427 19.6 mg, 90% 566 (M + 1)</p>
	
	<p>Example 438 23.2 mg, 90% 600 (M + 1)</p>

TABLE 2-5-continued

basic structure	
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$	
	Example 444 19.2 mg, 91% 578 (M + 1)
Ry	Rx
	
	Example 428 36.6 mg, 97% 534 (M + 1)
	Example 433 26.6 mg, 96% 534 (M + 1)
	Example 439 27.9 mg, 97% 568 (M + 1)
	

upper line: Example No.

middle line: yield, LC-MS purity (220 nm)

lower line: MS (ESI+, m/e)

TABLE 2-6

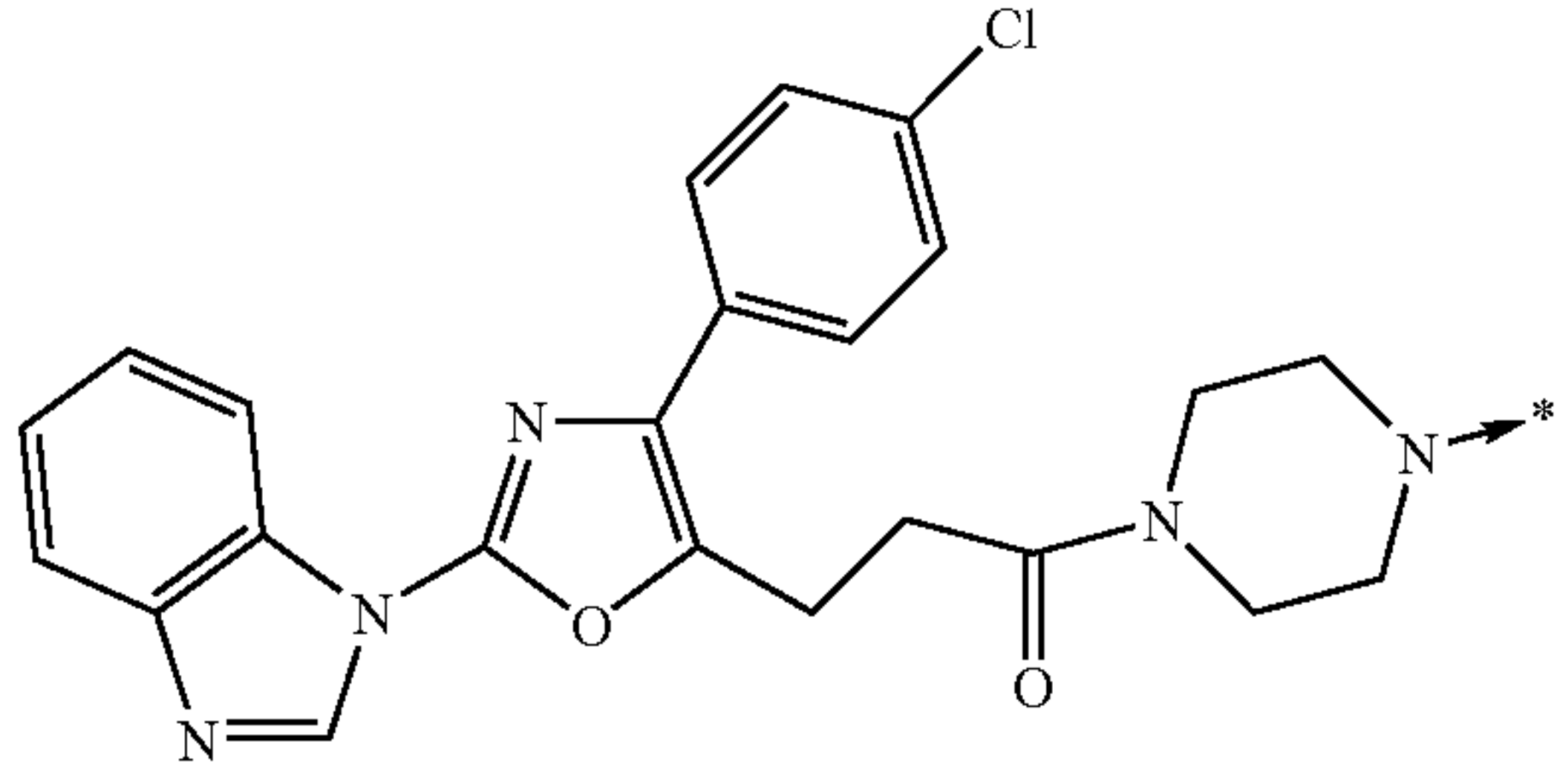
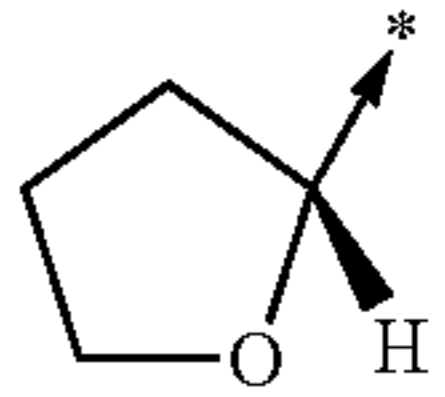
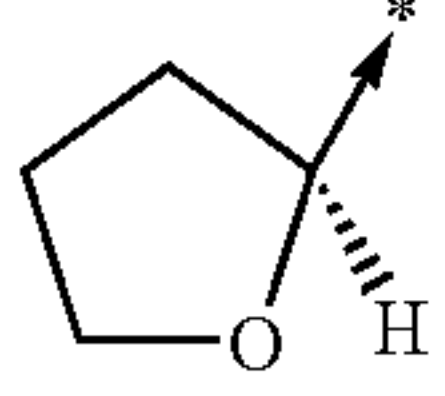
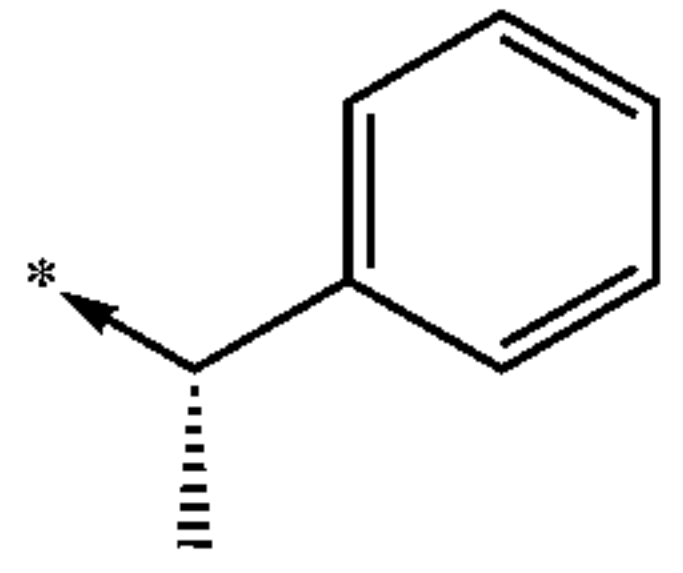
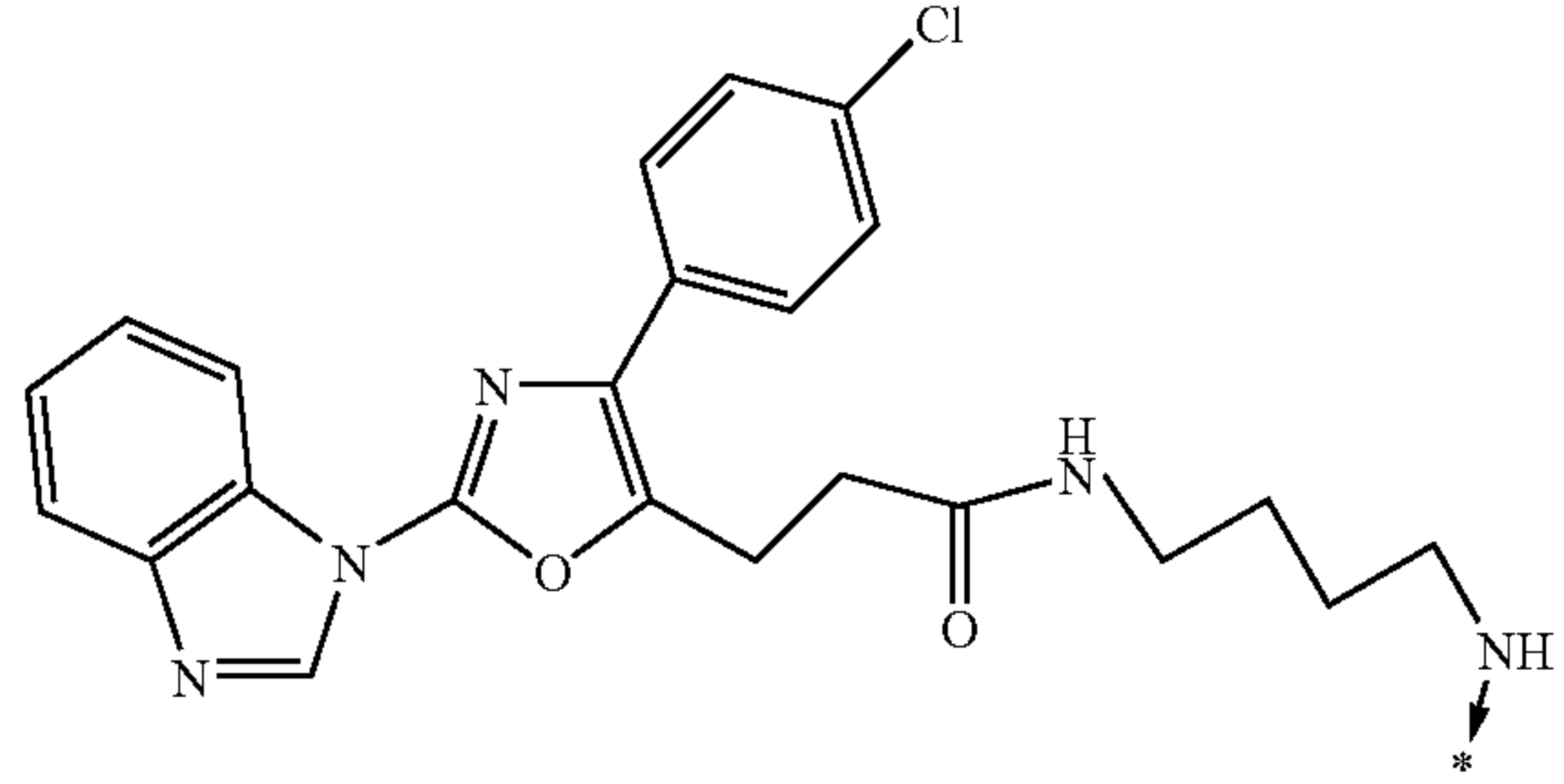
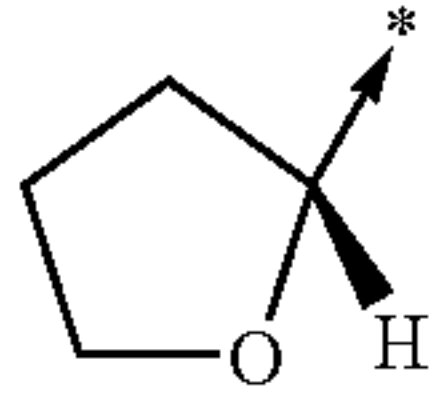
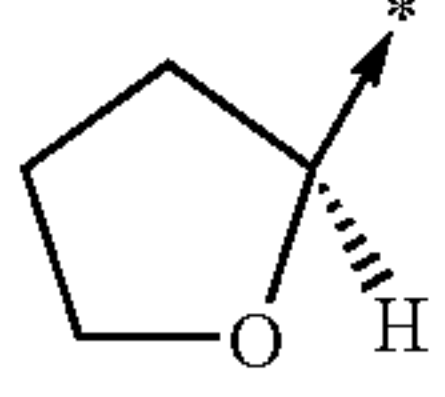
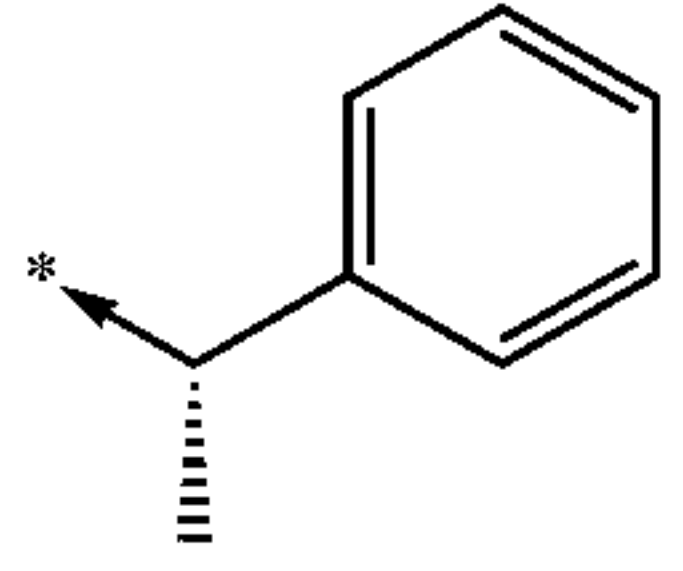
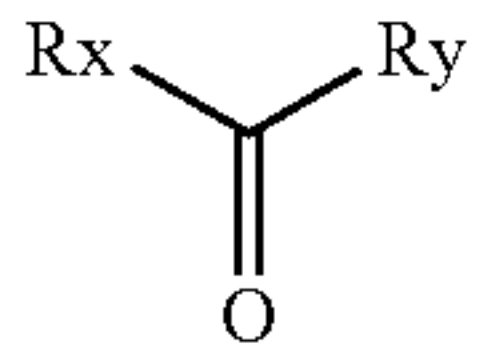
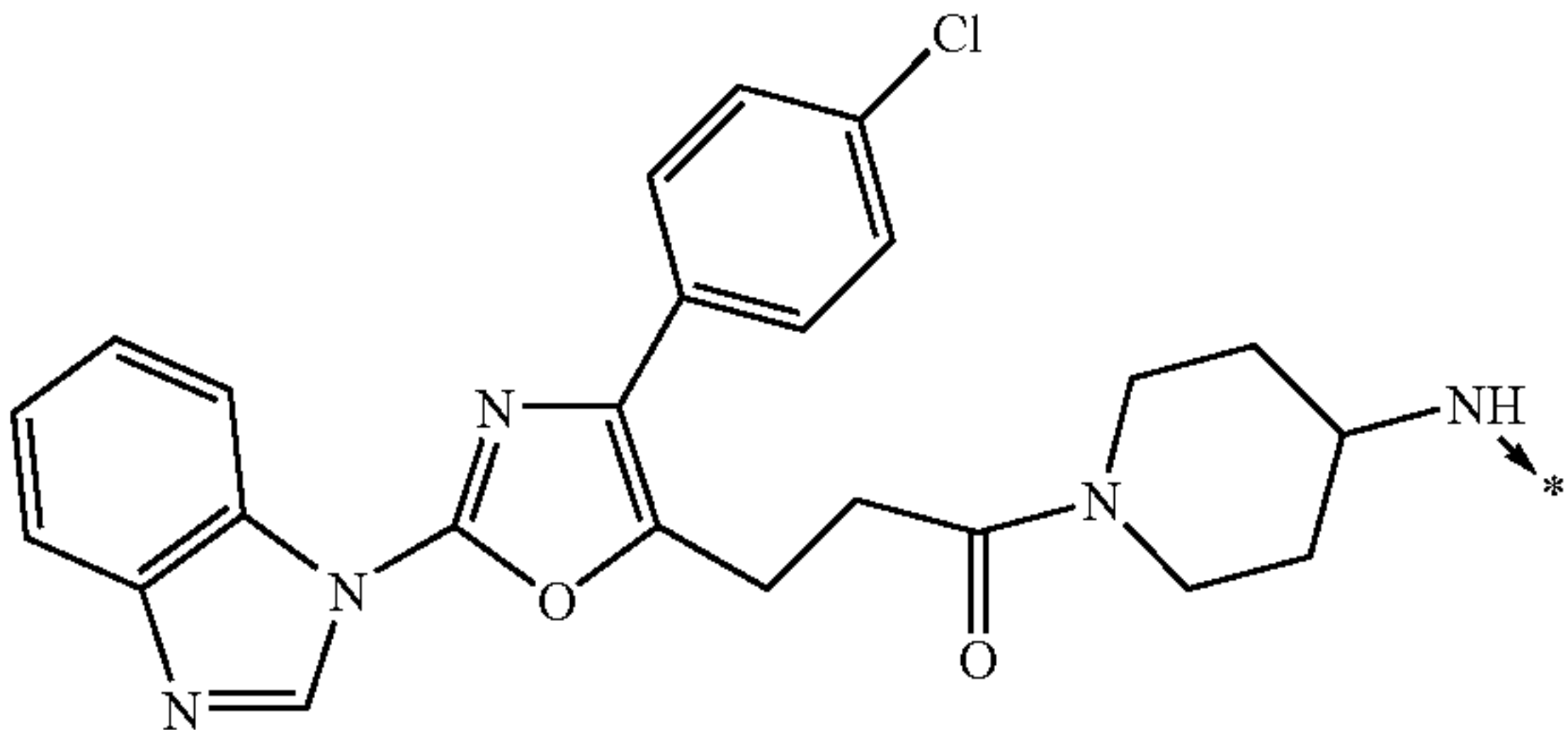
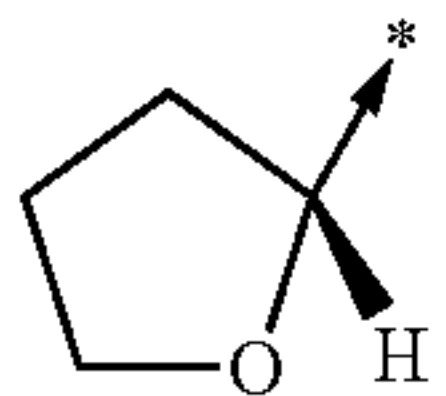
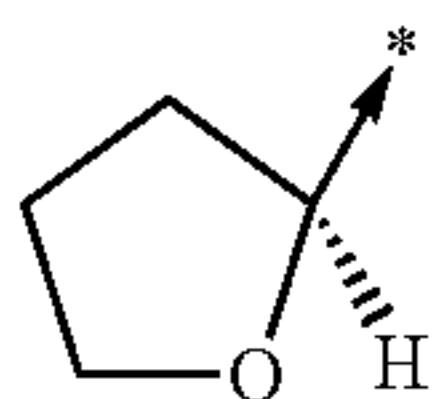
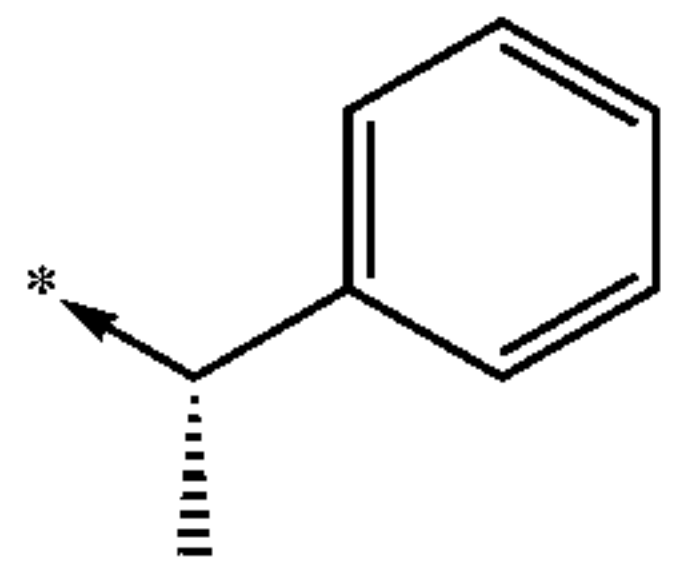
basic structure	
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$	
Ry	Rx
	
	<p>Example 429 23.5 mg, 93% 534 (M + 1)</p>
	<p>Example 434 19.7 mg, 94% 534 (M + 1)</p>
	<p>Example 440 20.2 mg, 97% 568 (M + 1)</p>
Ry	Rx
	
	<p>Example 430 33.7 mg, 82% 536 (M + 1)</p>
	<p>Example 435 28 mg, 88% 536 (M + 1)</p>
	<p>Example 441 28.5 mg, 91% 570 (M + 1)</p>

TABLE 2-6-continued

basic structure	
Ry	Rx
	
	
	<p>Example 431 33.5 mg, 93% 548 (M + 1)</p>
	<p>Example 436 26.1 mg, 88% 548 (M + 1)</p>
	<p>Example 442 25.6 mg, 94% 582 (M + 1)</p>

upper line: Example No.
middle line: yield, LC-MS purity (220 nm)
lower line: MS (ESI+, m/e)

TABLE 2-7

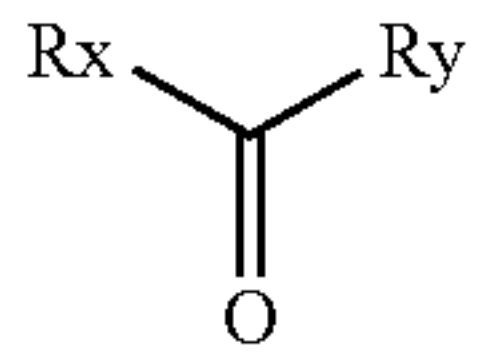
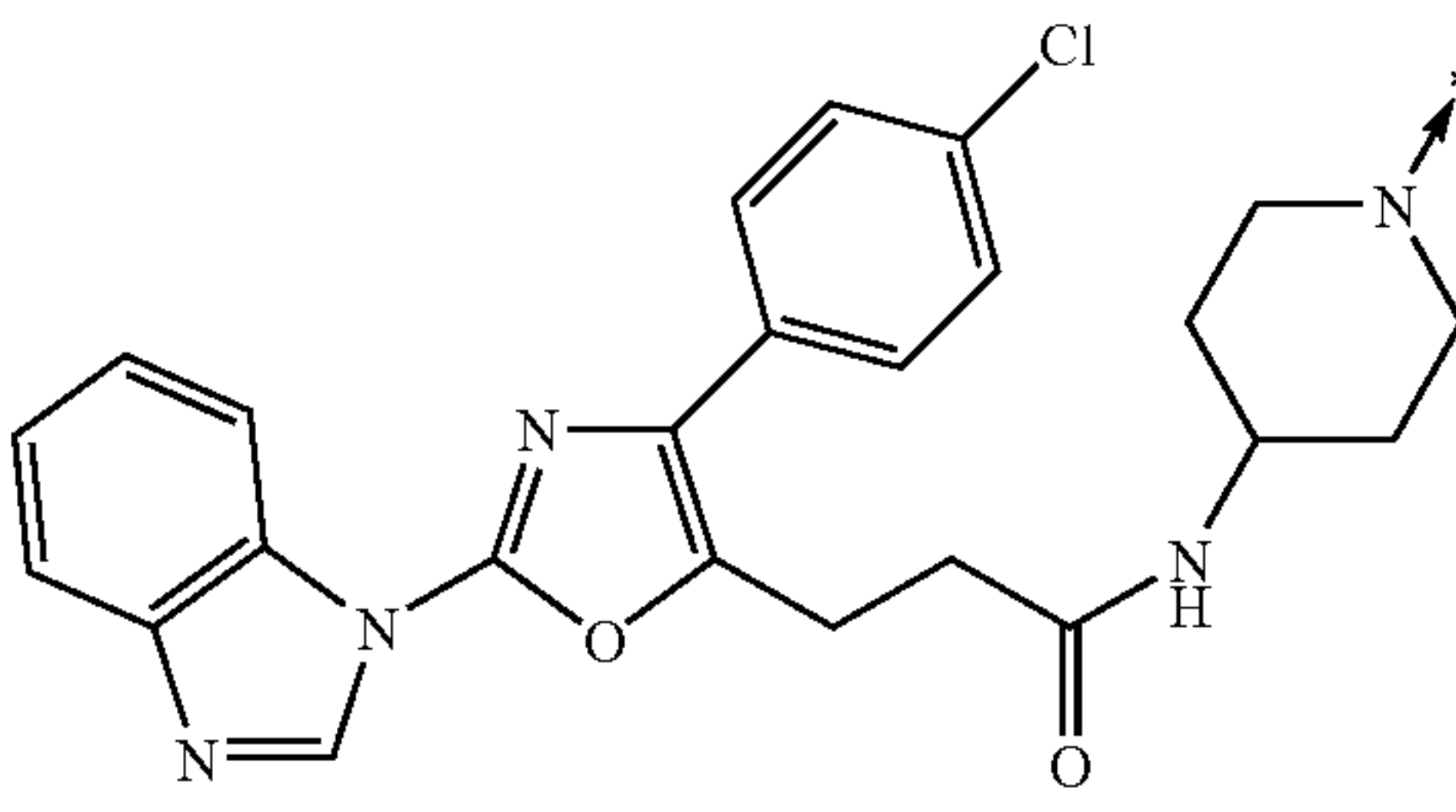
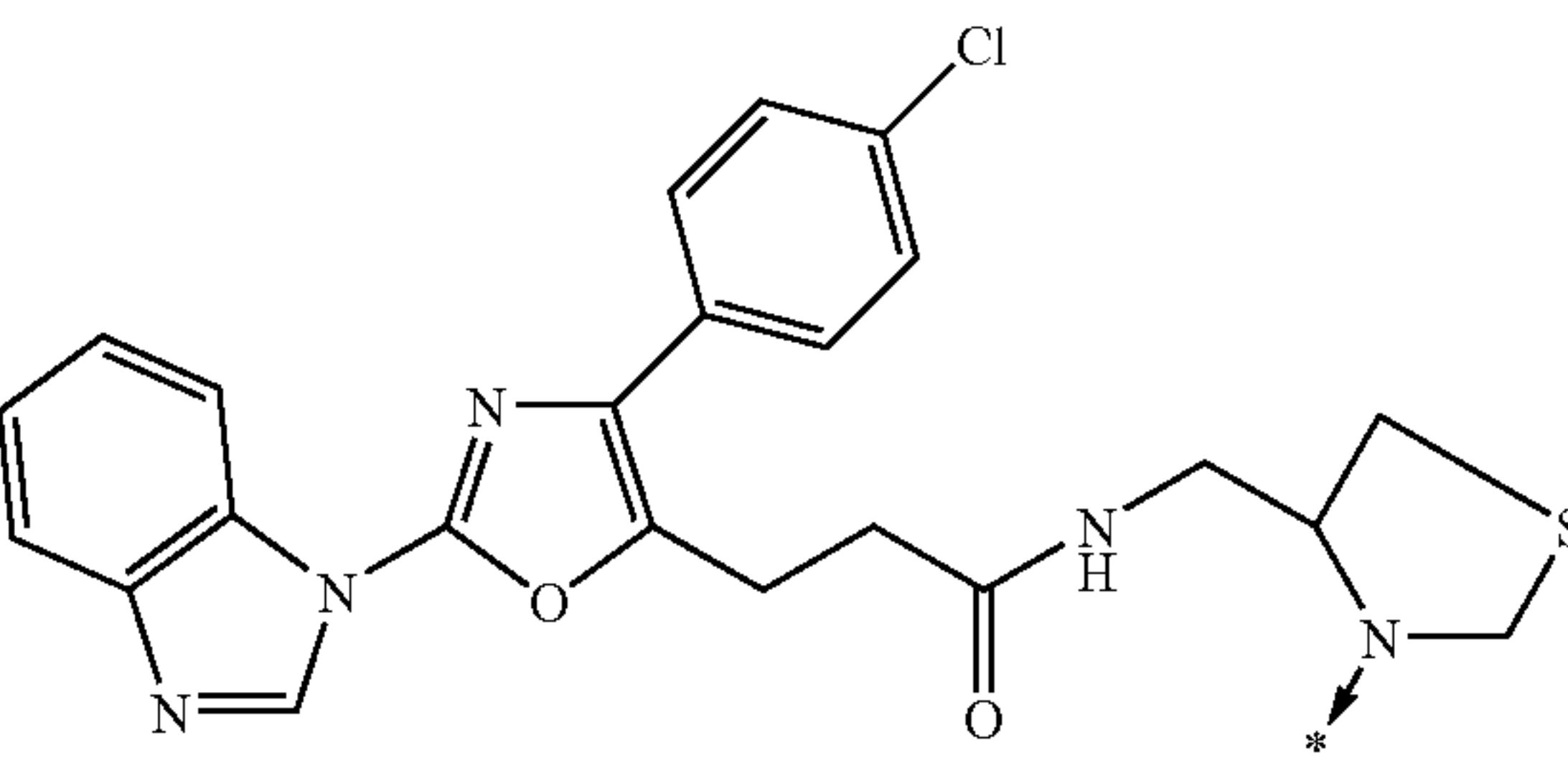
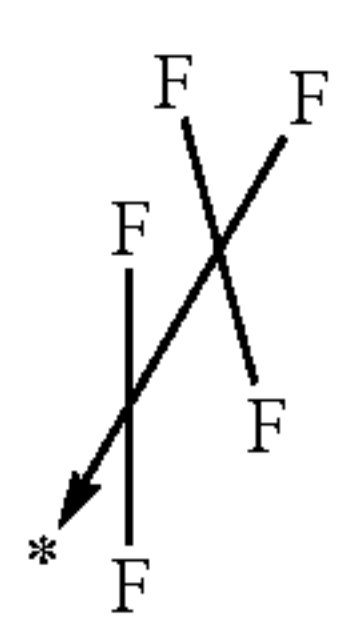
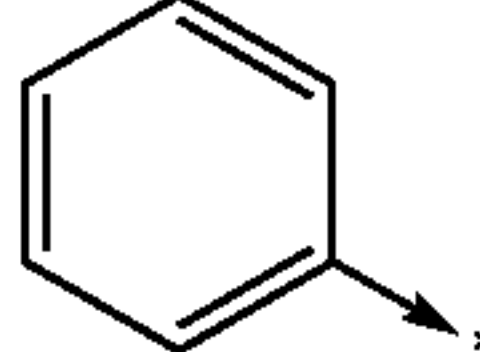
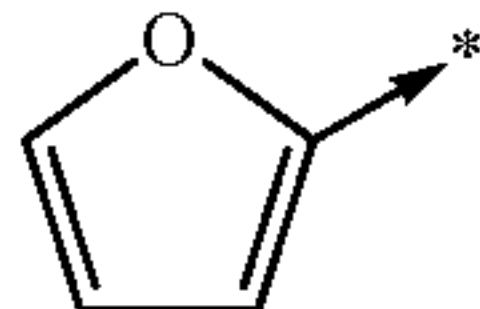
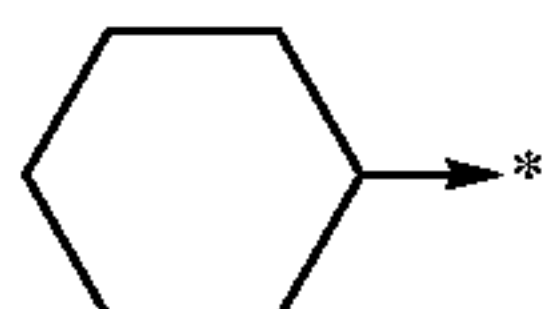
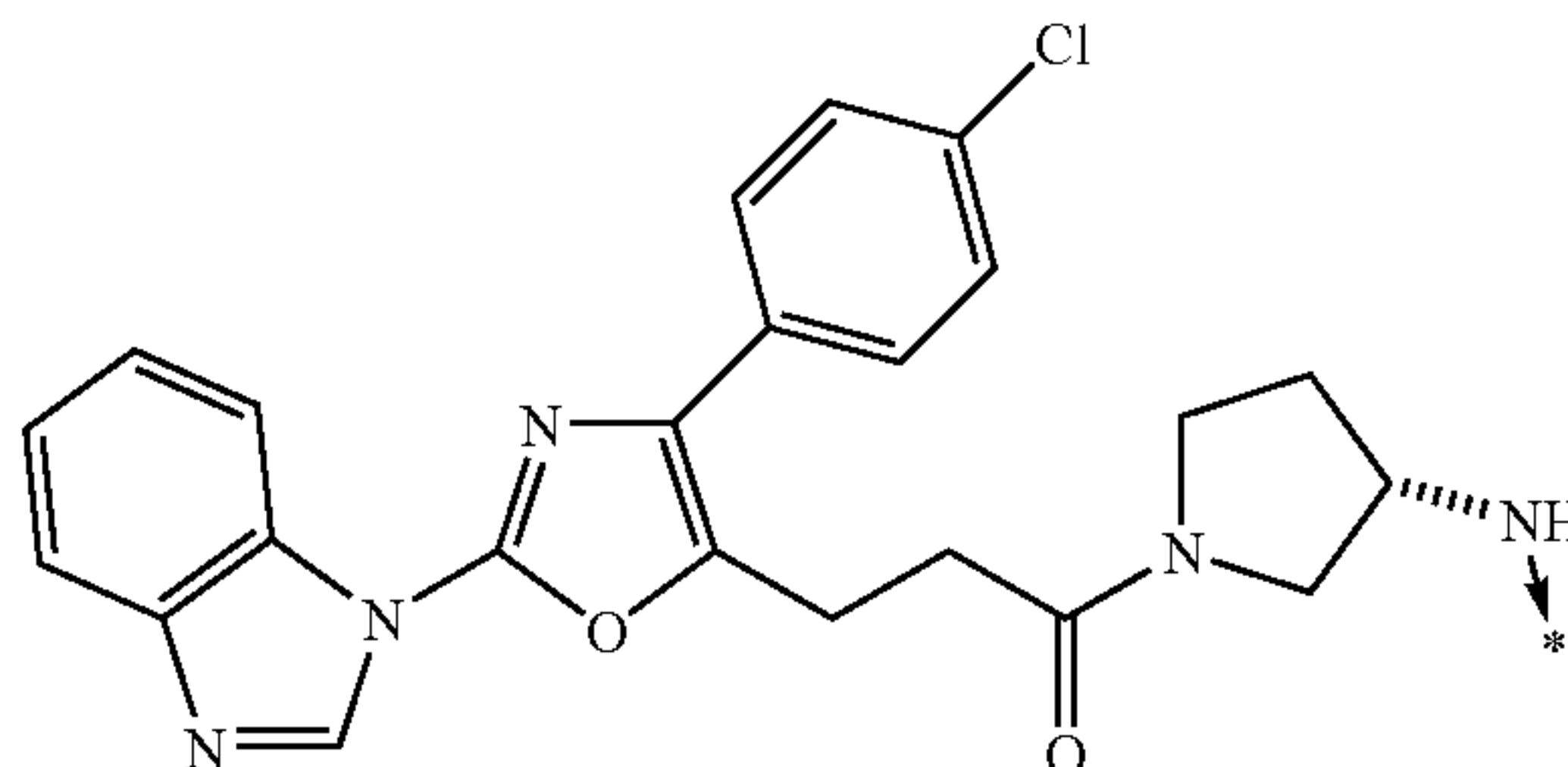
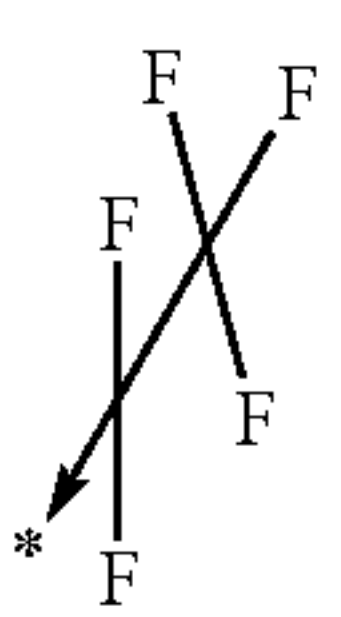
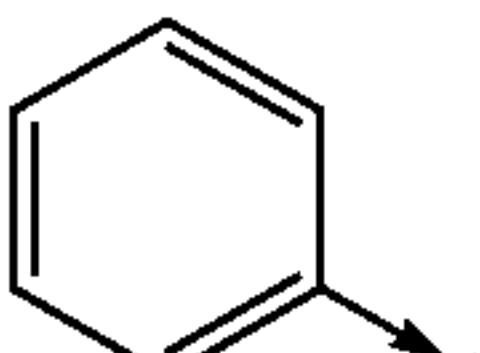
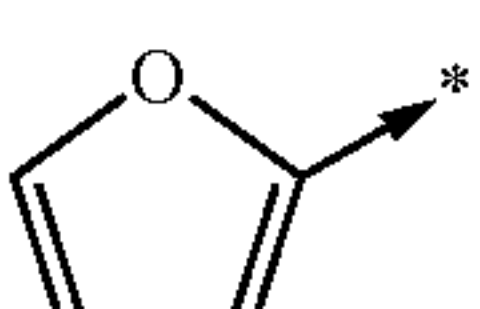
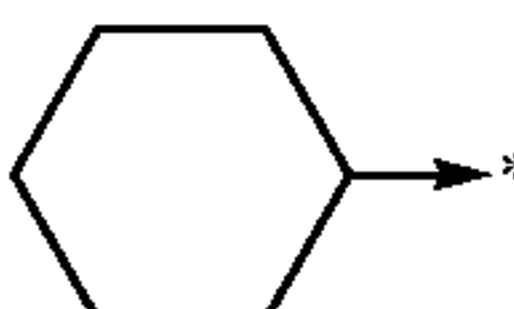
basic structure	
Ry	Rx
	
	
	
	<p>Example 445 19.2 mg, 89% 610(M + 1)</p>

TABLE 2-7-continued

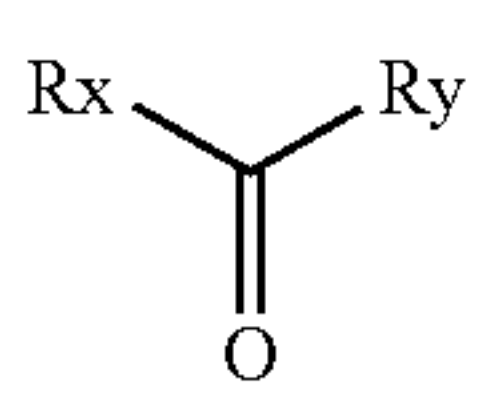
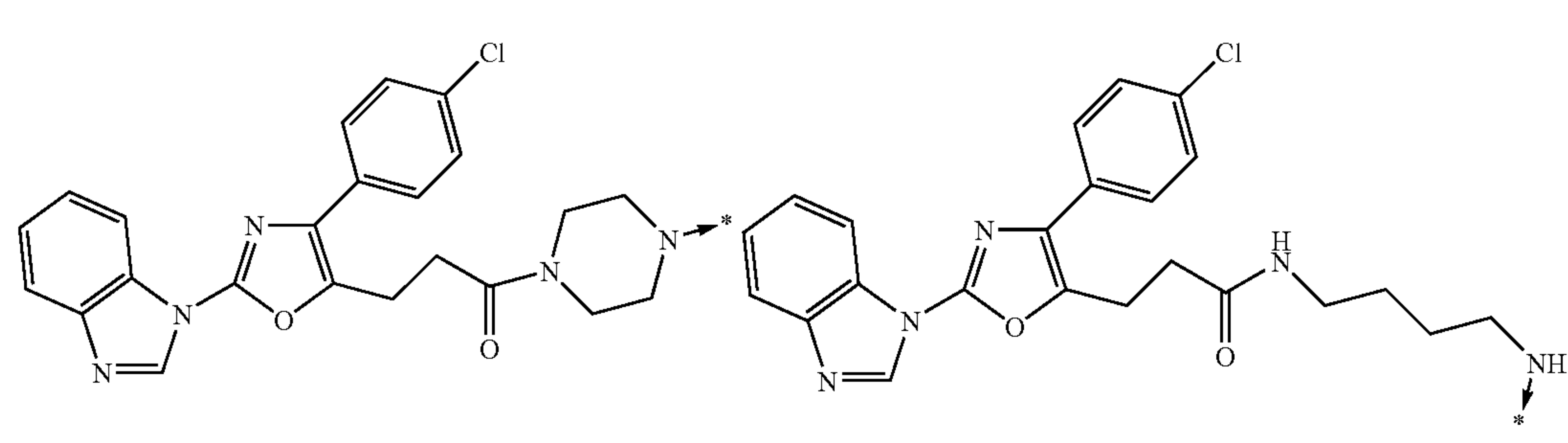
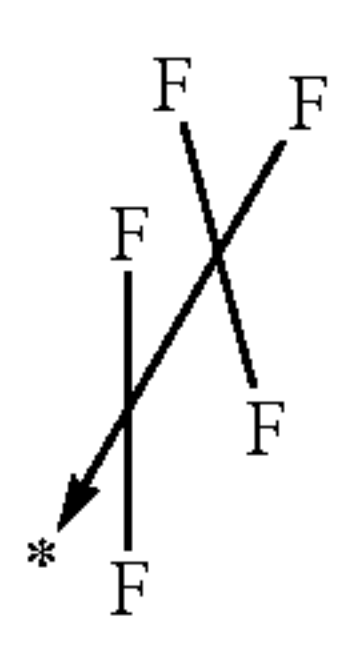
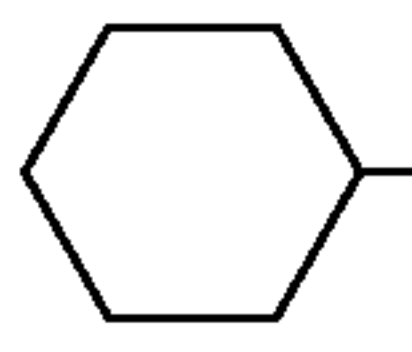
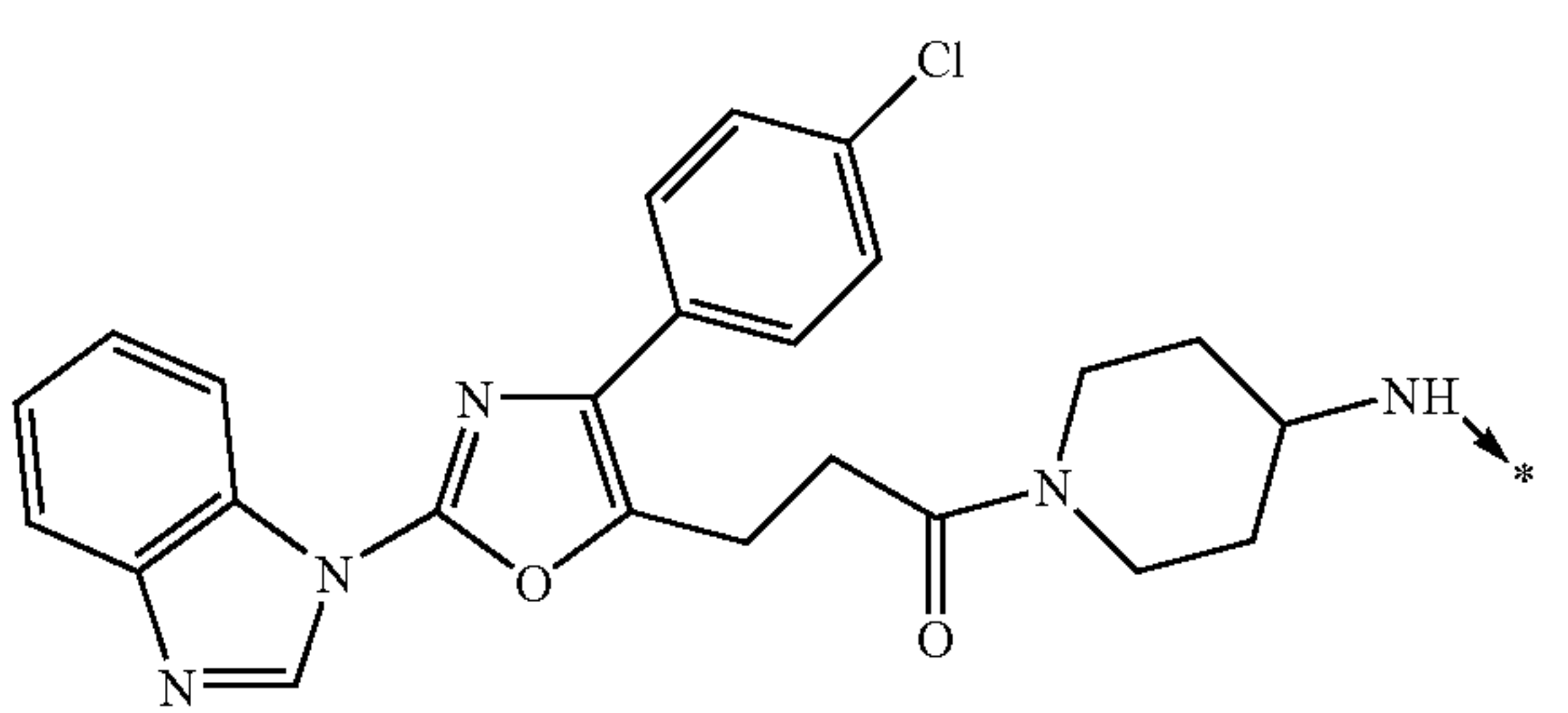
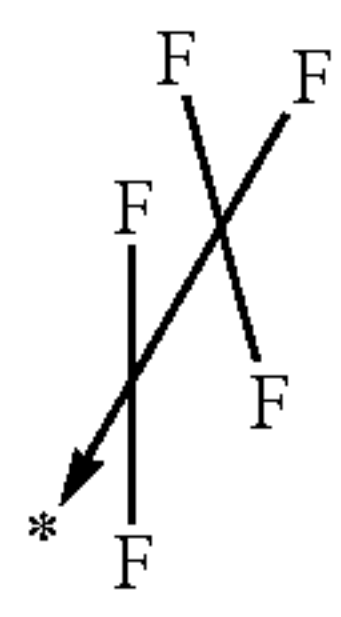
		basic structure	
		$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$	
	Example 449 24.4 mg, 94% 568(M + 1)		Example 450 43.1 mg, 89% 572(M + 1)
	Example 451 38.9 mg, 97% 558(M + 1)		Example 452 28.1 mg, 83% 562(M + 1)
			
		Rx	
		Ry	
			Example 446 28.8 mg, 92% 582(M + 1)
			
			
			Example 453 2.1 mg, 80% 546(M + 1)

upper line: Example No.

middle line: yield, LC-MS purity(220 nm)

lower line: MS (ESI+, m/e)

TABLE 2-8

basic structure	
	
	Rx
Ry	
	<p>Example 447 25.6 mg, 88% 584(M + 1)</p>
	<p>Example 454 5 mg, 92% 546(M + 1)</p>
	Rx
Ry	
	<p>Example 448 23.6 mg, 90% 596(M + 1)</p>

upper line: Example No.

middle line: yield, LC-MS purity(220 nm)

lower line: MS(ESI+, m/e)

A mixture of 2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolepropionic acid (37 mg), 4-(2-cyanoethyl)piperazine (20 mg), 1-hydroxy-7-azabenzotriazole (20 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (20 mg) and N,N-dimethylformamide (1 ml) was shaken at room temperature for 8 hrs. The reaction mixture was directly poured into preparative HPLC and purified to give the object compound.

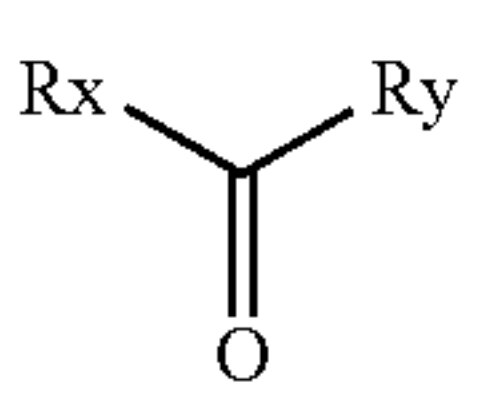
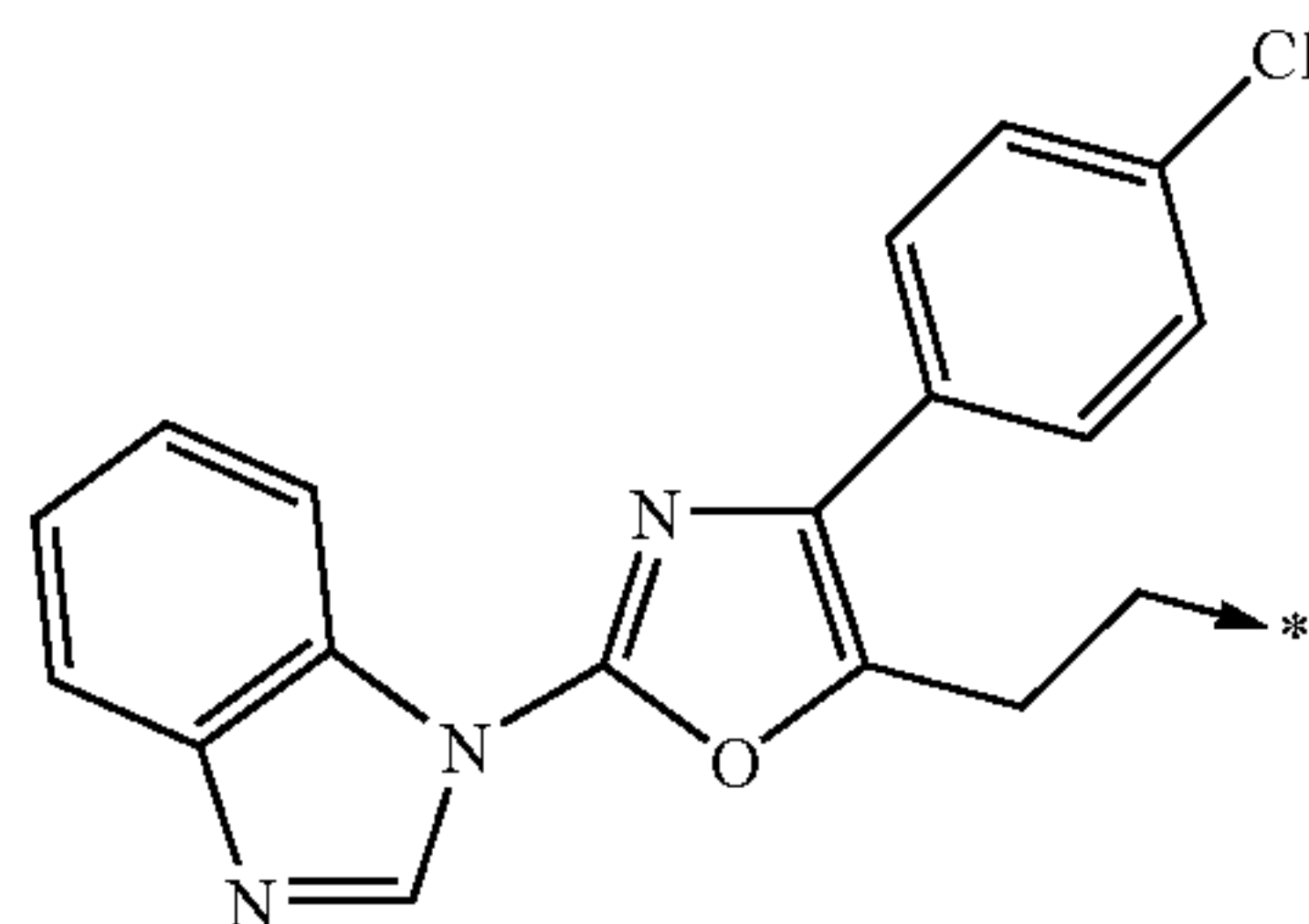
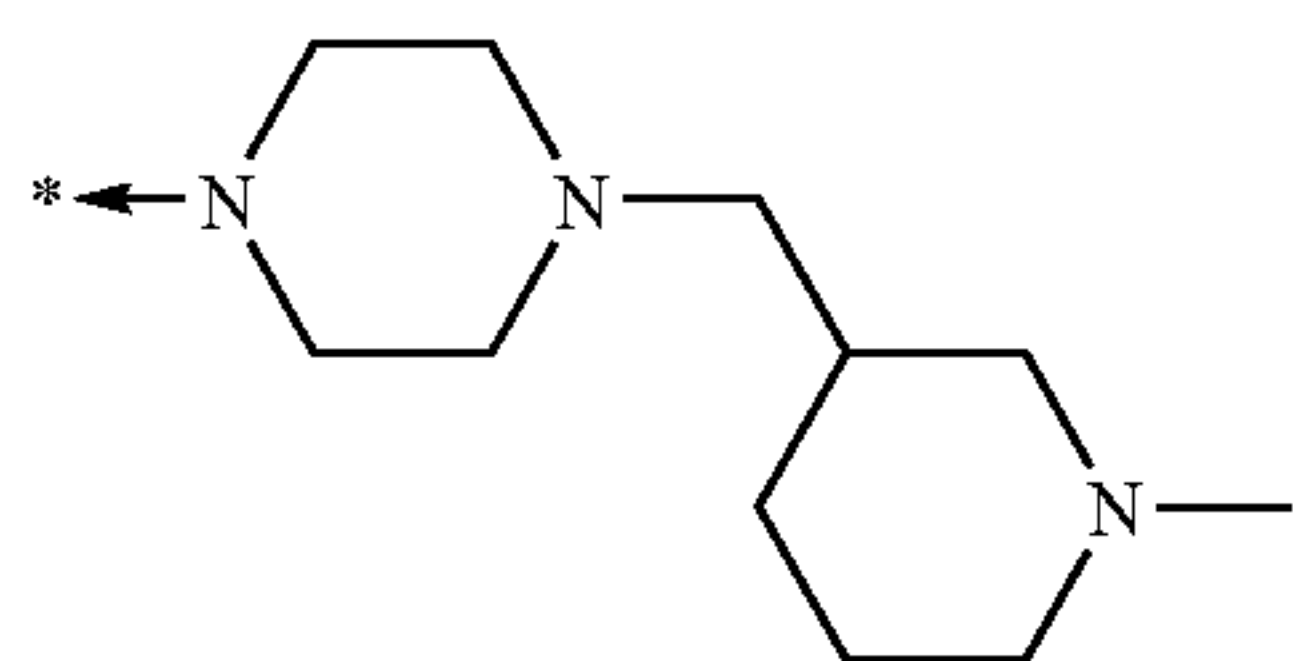
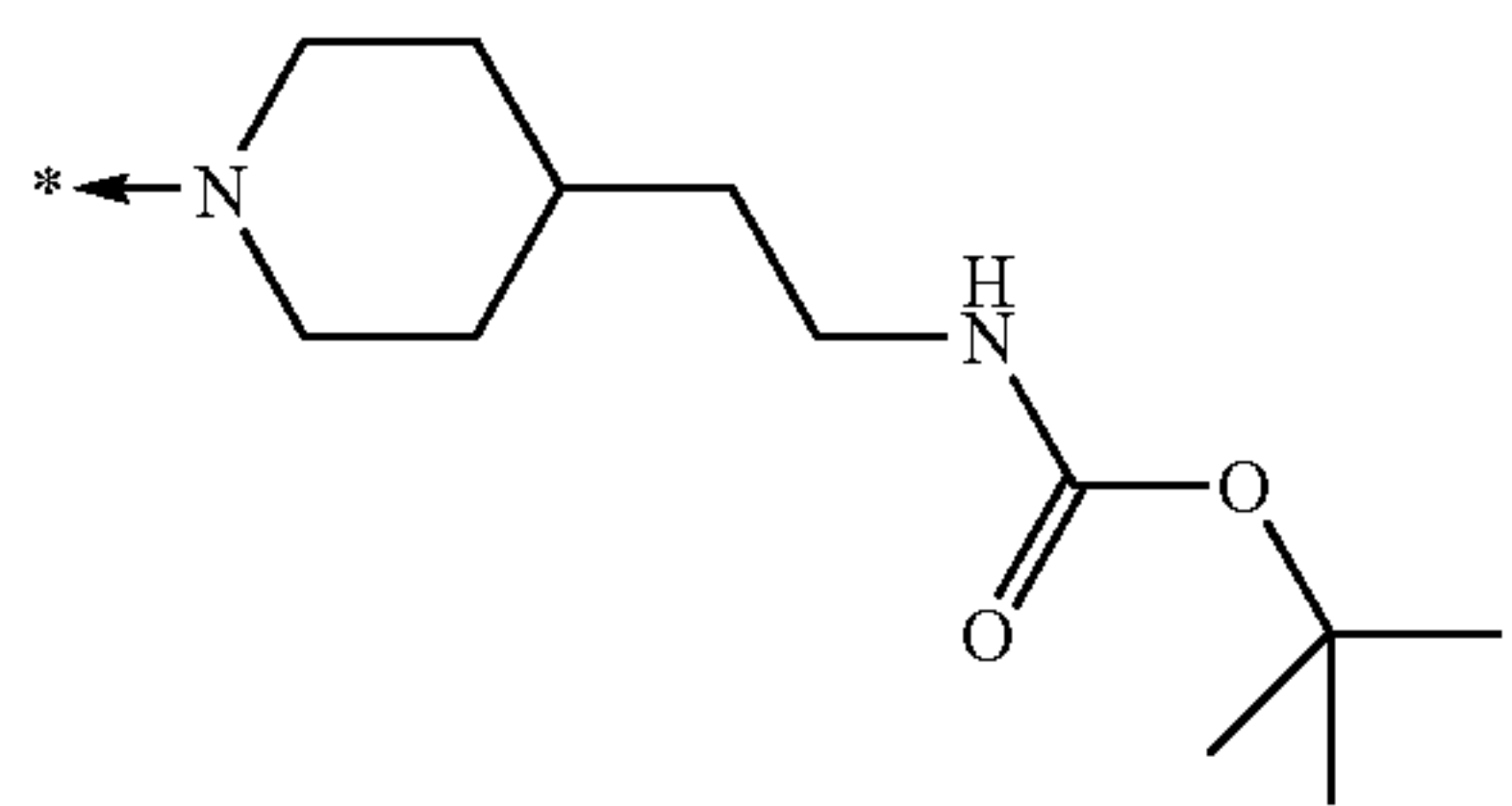
In the same manner as in Example 455, the object compounds were obtained.

The structure and purity of the object compounds of Examples 455–461 were confirmed by LC-MS, HPLC. The yield, structure, purity and mass spectrum data of the object compounds are shown in [Table 3].

TABLE 3

basic structure	
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$	
	Rx
Ry	
	Example 455 30.4 mg, 95% 489(M + 1)
	Example 456 7.7 mg, 94% 547(M + 1)
	Example 457 10 mg, 99% 528(M + 1)
	Example 458 13.5 mg, 93% 566(M + 1)
	Example 459 20 mg, 97% 538(M + 1)

TABLE 3-continued

basic structure	
	
Rx	
Ry	
	<p>Example 460 32.9 mg, 99% 547(M + 1)</p>
	<p>Example 461 18.5 mg, 94% 578(M + 1)</p>

upper line: Example No.
middle line: yield, LC-ms purity(220 nm)
lower line: MS(ESI+, m/e)

Example 462

A mixture of 4-(4-chlorophenyl)-2-phenyl-5-oxazolebutanoic acid (35 mg), N,N-dimethylethylenediamine (15 mg), 1-hydroxy-7-azabenzotriazole (20 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (20 mg) and N,N-dimethylformamide (1 ml) was shaken at room temperature for 8 hrs. The reaction mixture was directly poured into preparative HPLC and purified to give the object compound.

Examples 463–502

In the same manner as in Example 462, the object compounds were obtained.

The structure and purity of the object compounds of Examples 462–502 were confirmed by LC-MS, HPLC. The structure, purity (HPLC retention time) and mass spectrum data of the object compounds are shown in [Table 4-1]–[Table 4-5].

TABLE 4-1

basic structure	
	$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$
	Rx
Ry	
	Rx
Ry	
	Rx
Ry	
	Rx
Ry	
	Rx
Ry	
	Rx
Ry	

Example 462
100%, 3.366
412(M + 1)

Example 463
94%, 3.431
454(M + 1)

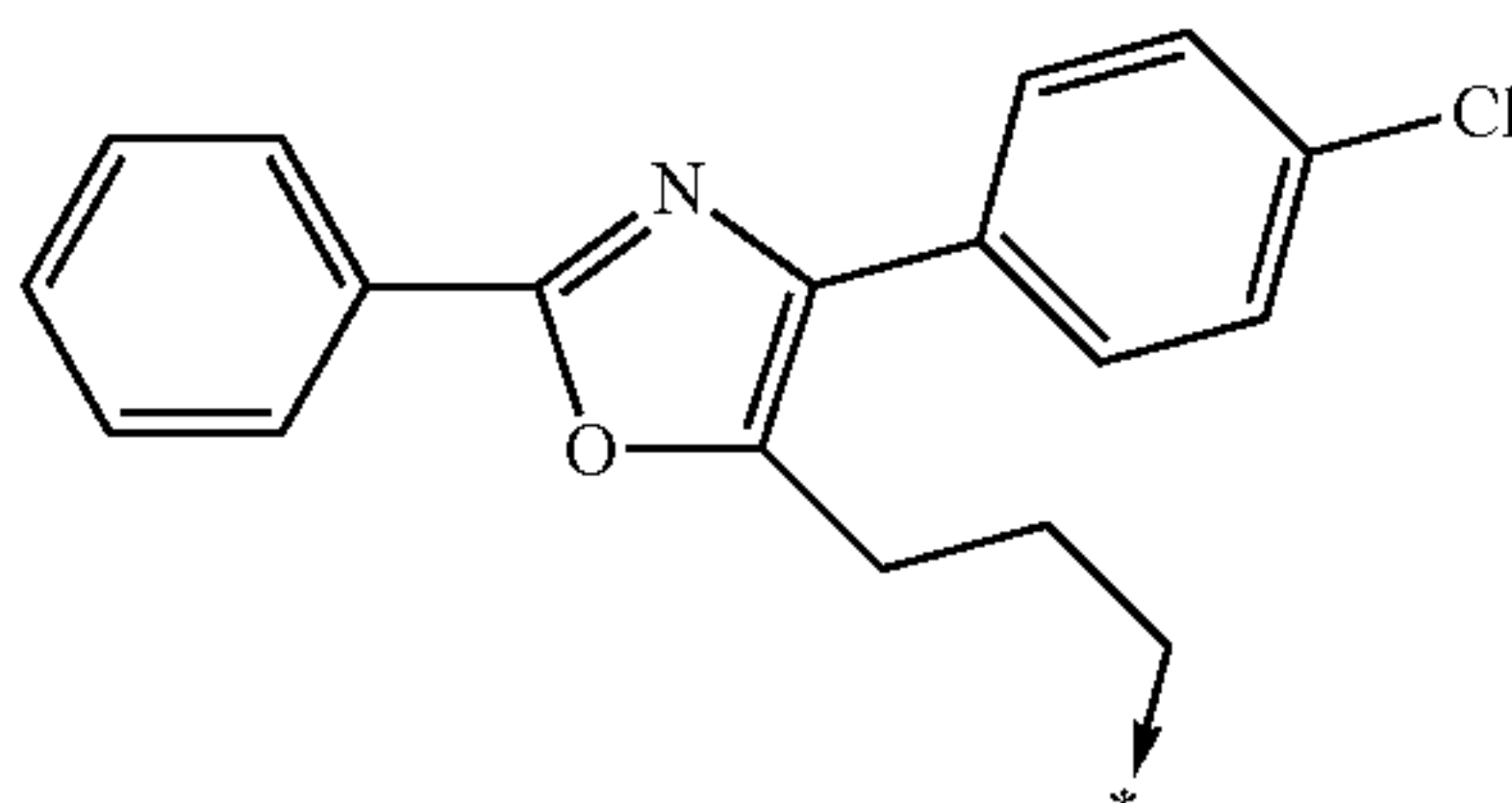
Example 464
98%, 3.463
452(M + 1)

Example 465
99%, 3.354
454(M + 1)

Example 466
100%, 3.08
481(M + 1)

Example 467
95%, 3.692
488(M + 1)

TABLE 4-1-continued

basic structure		
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \diagup \quad \diagdown \\ \text{O} \end{array}$		
	<p>Example 468 92%, 3.643 514(M + 1)</p>	<p>Example 469 99%, 3.482 480(M + 1)</p>

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 4-2

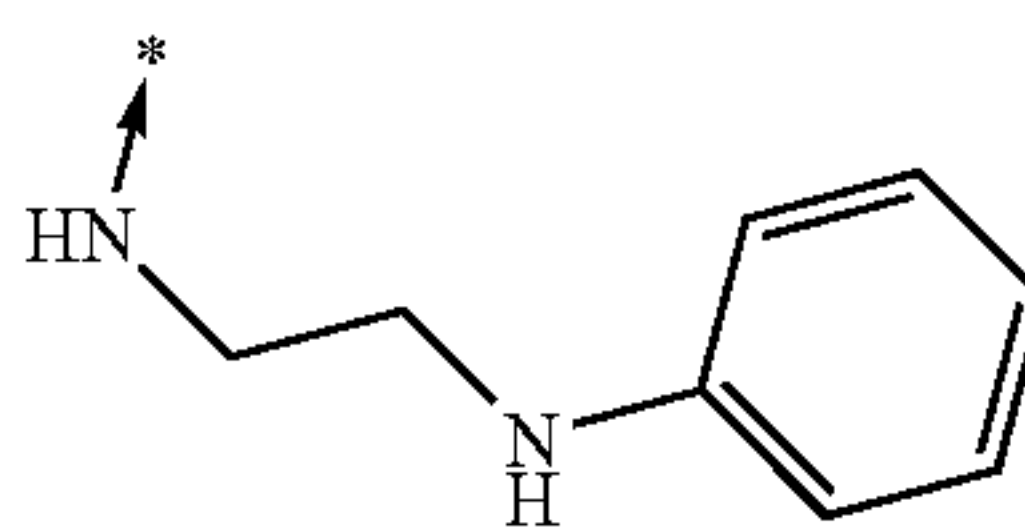
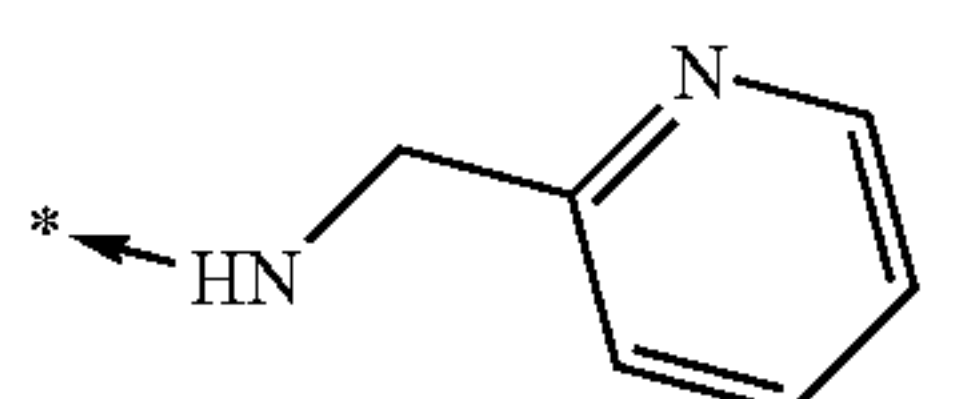
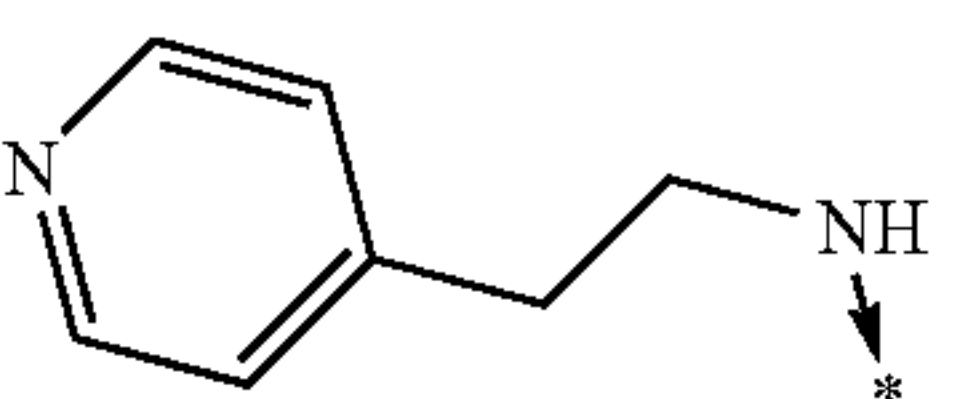
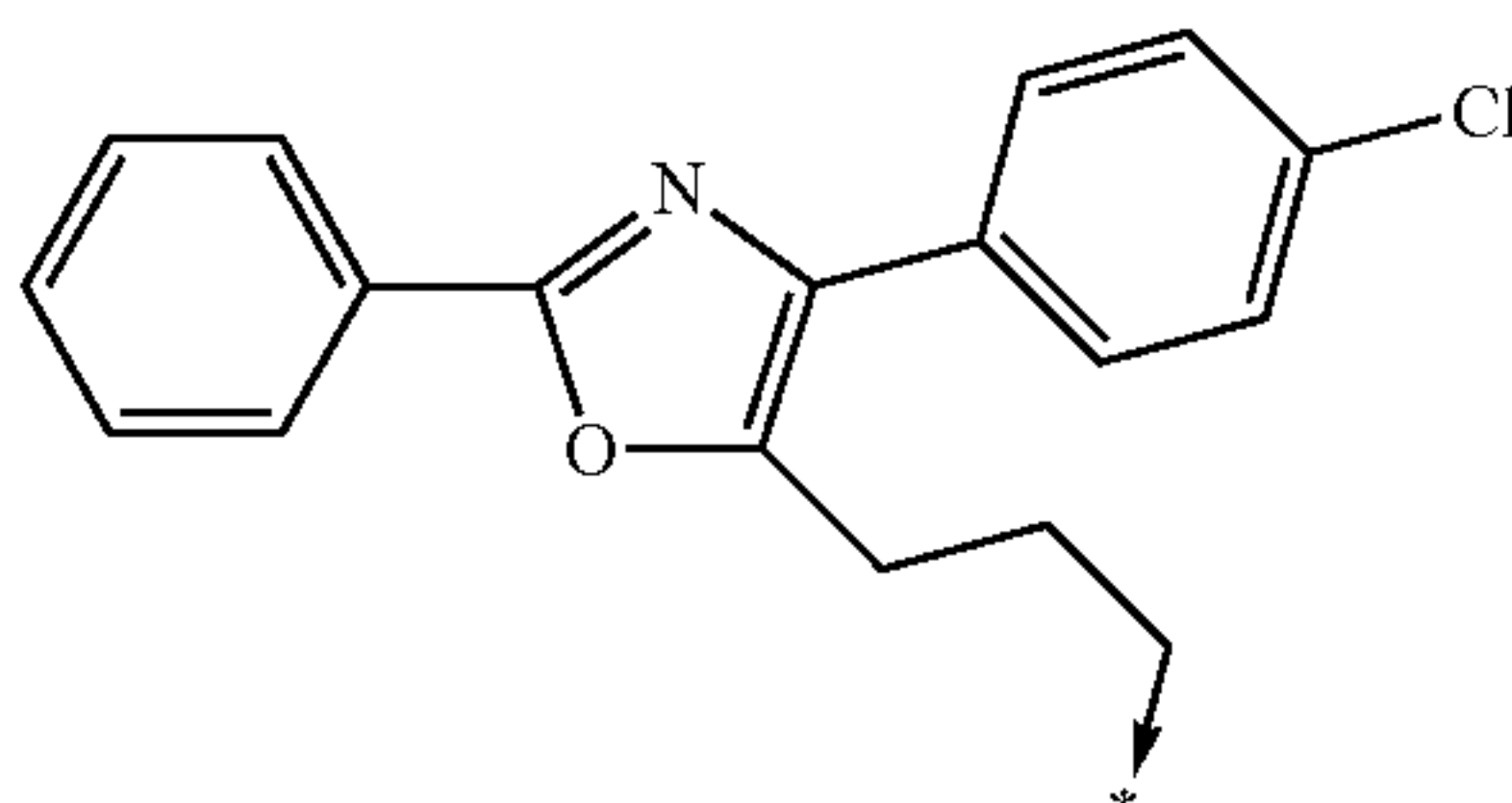
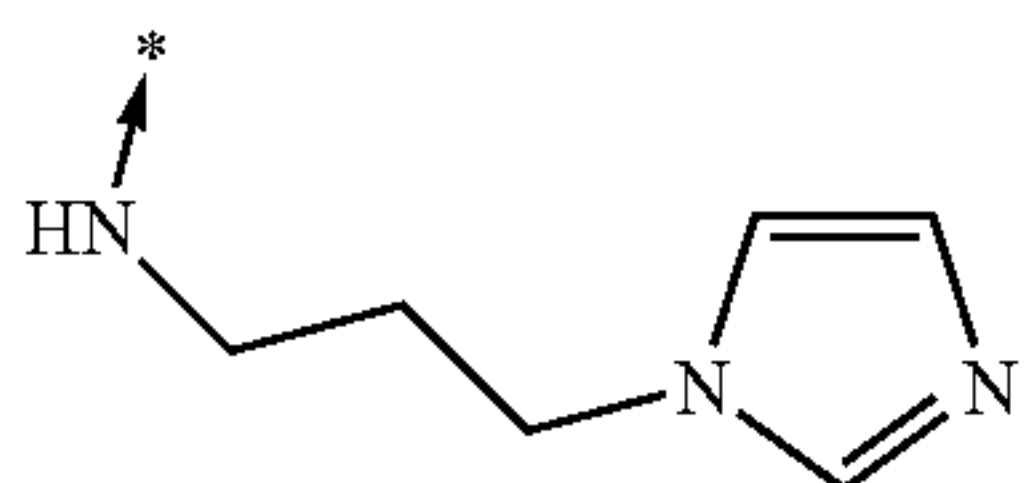
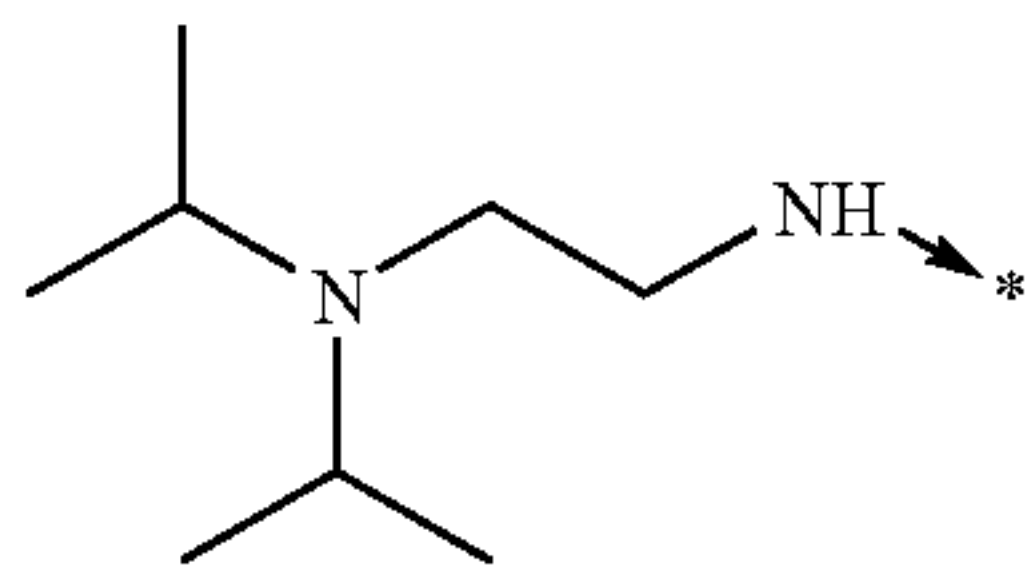
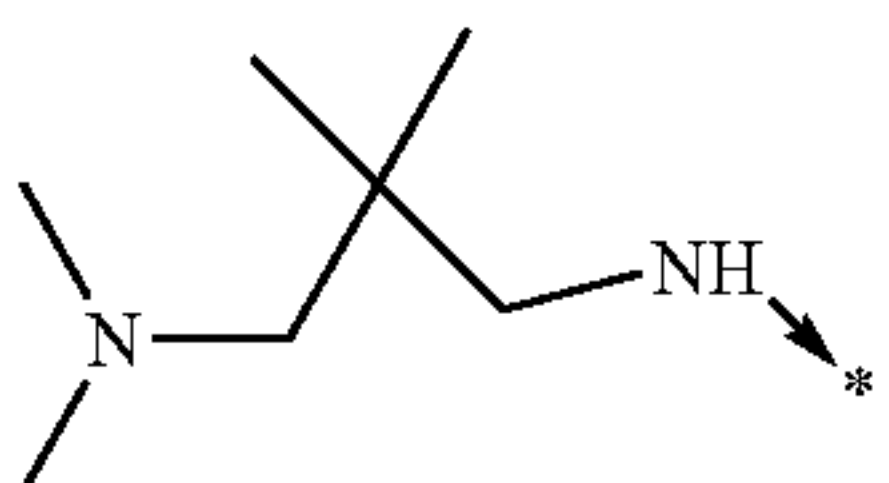
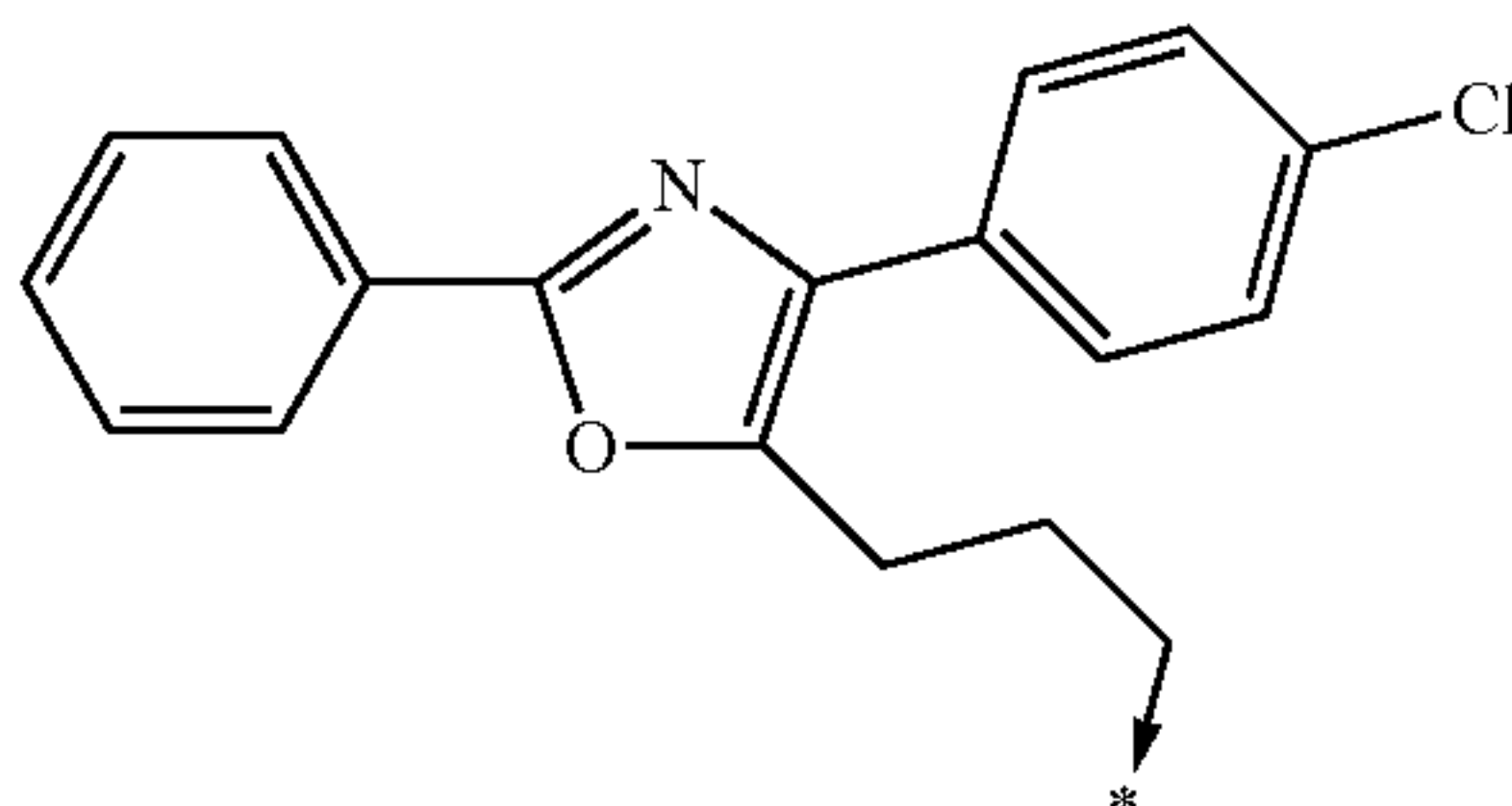
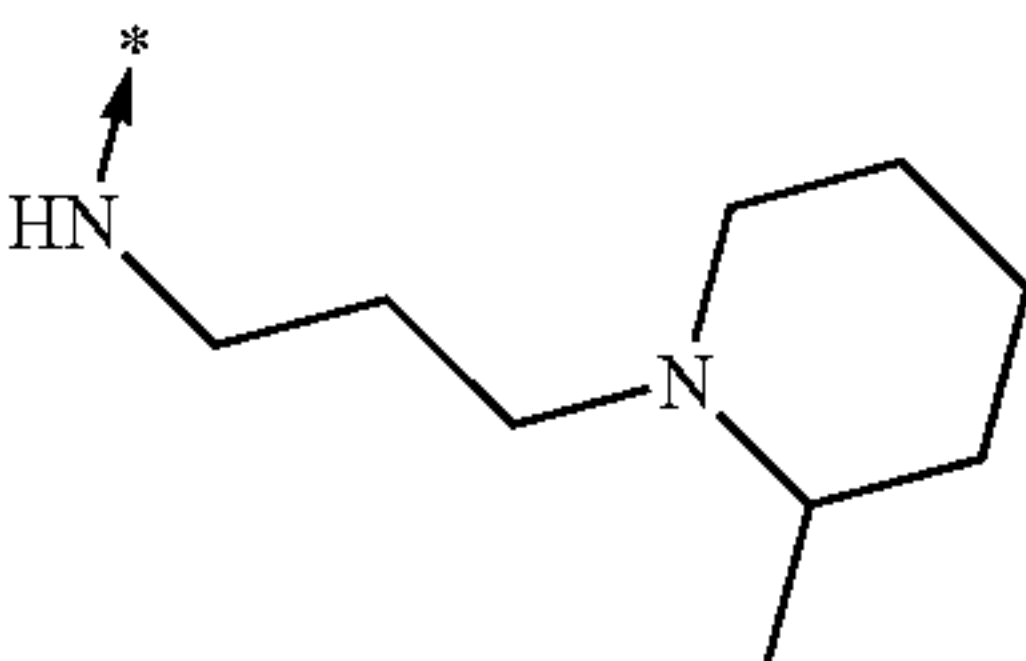
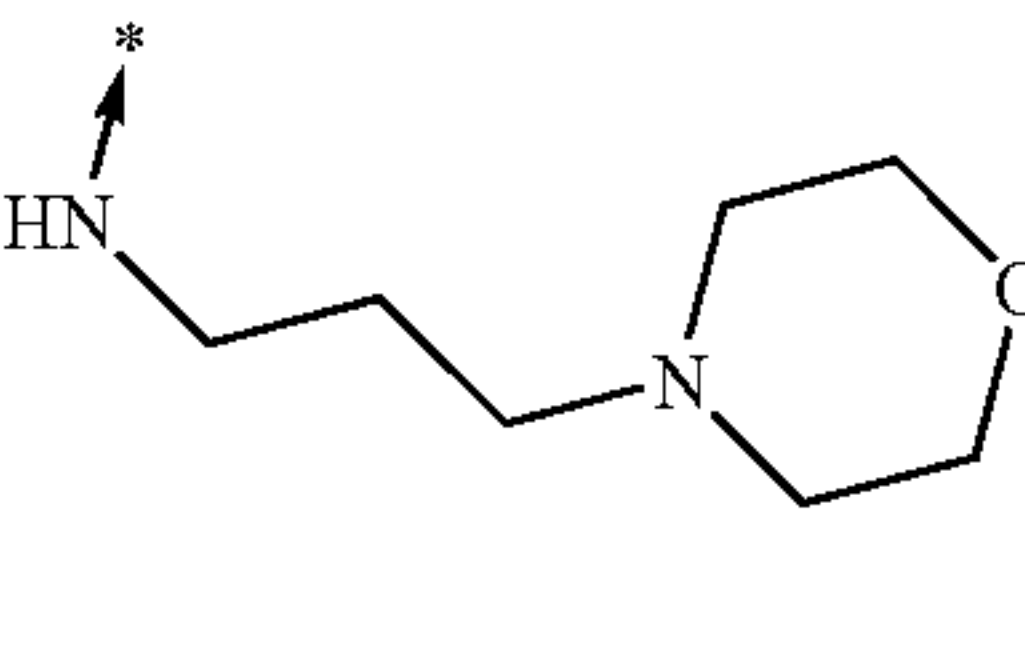
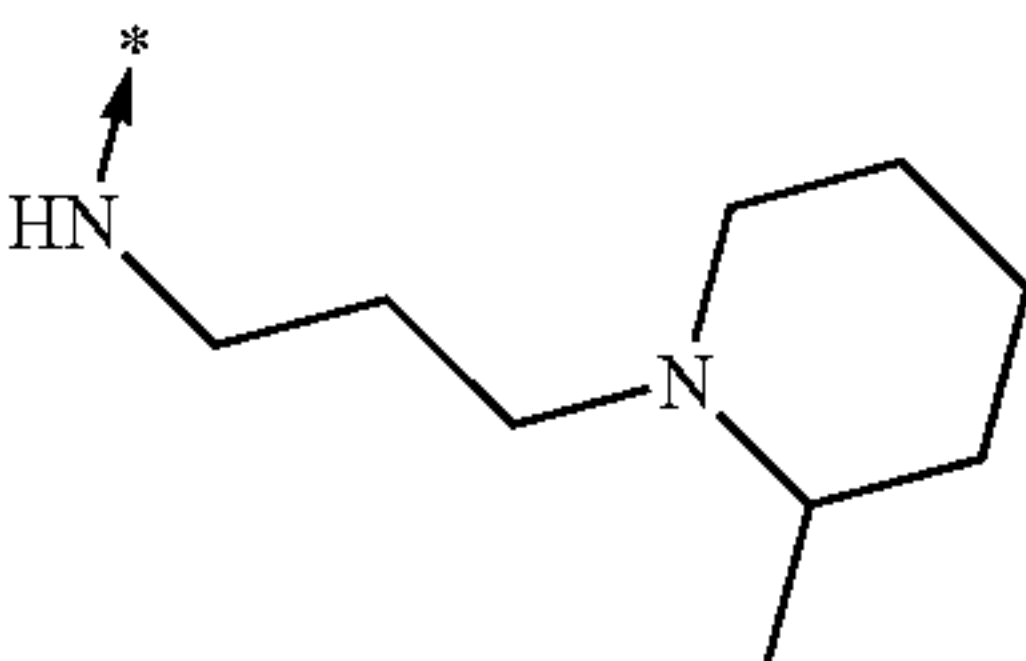
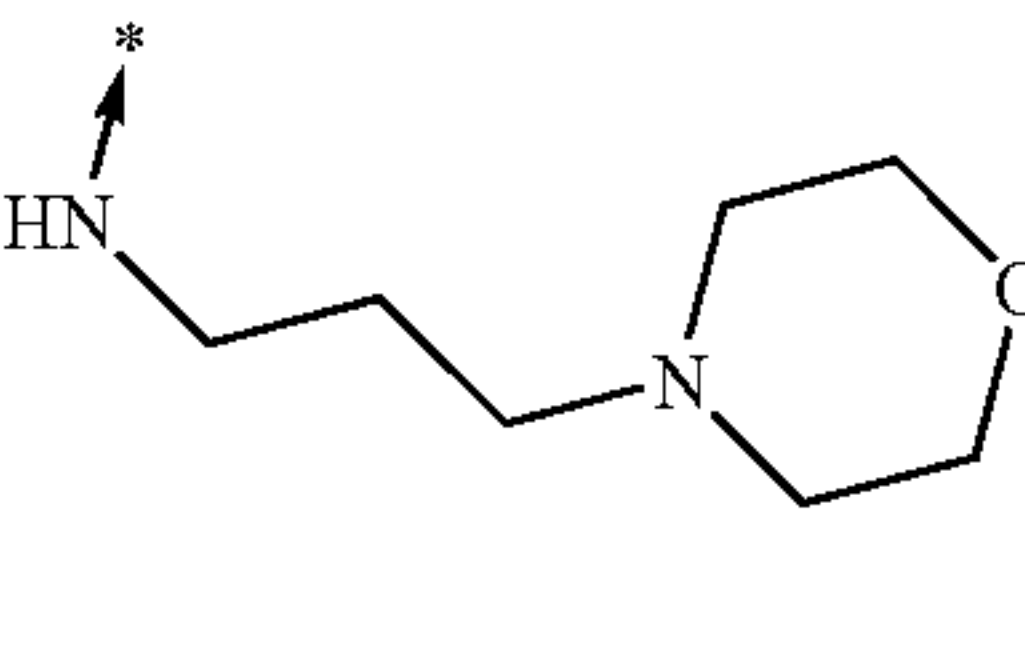
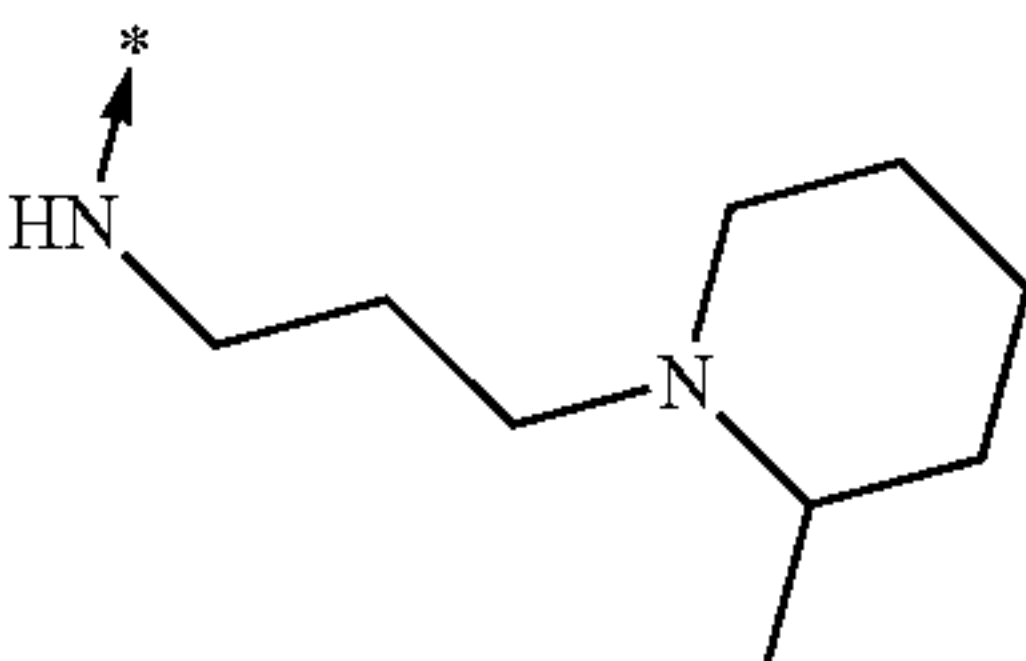
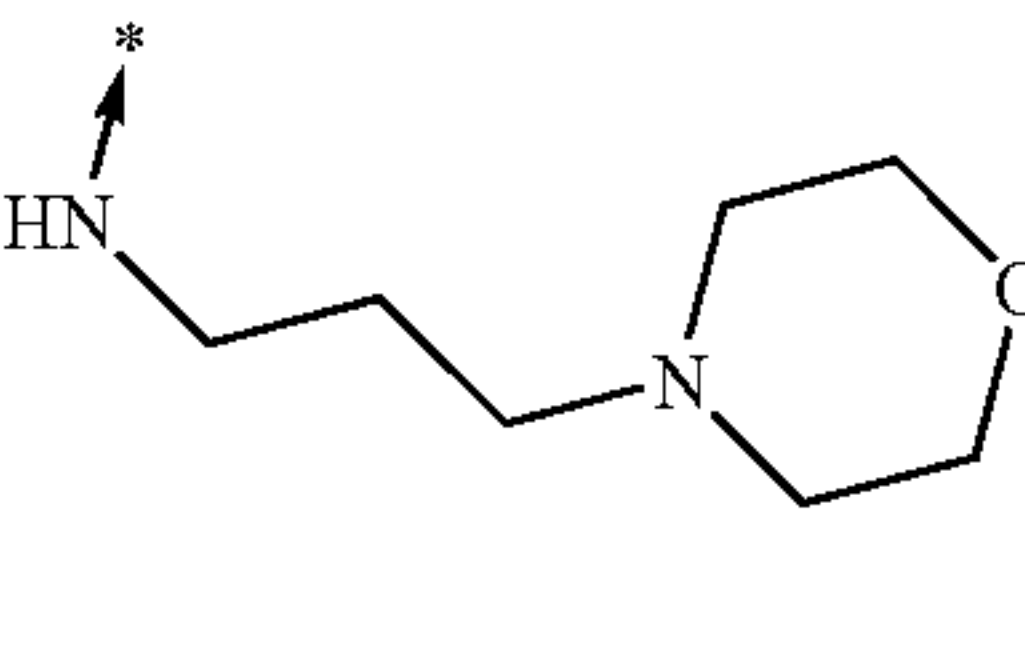
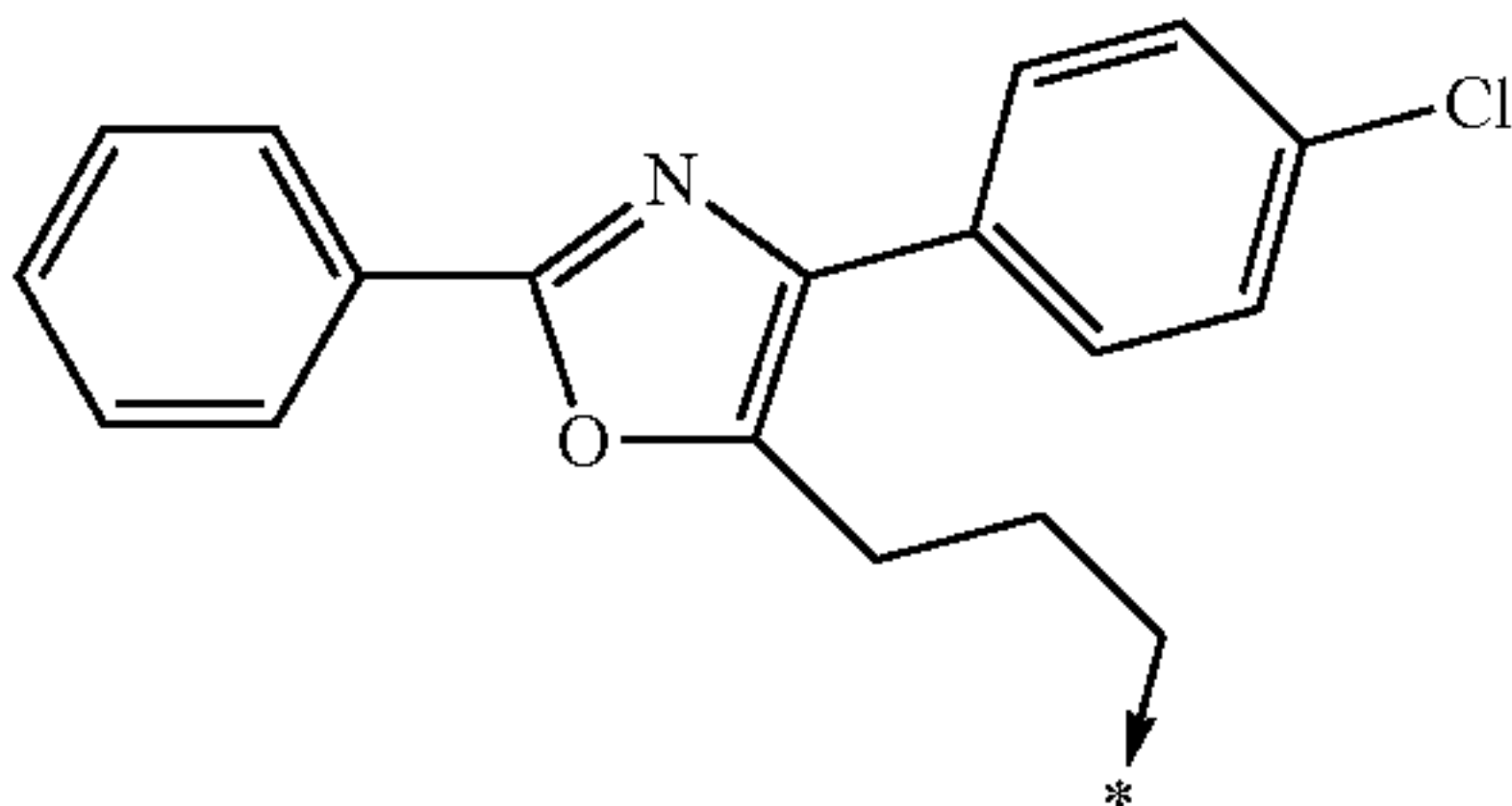
basic structure			
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \diagup \quad \diagdown \\ \text{O} \end{array}$			
	Rx		
Ry			
	<p>Example 470 98%, 3.946 460(M + 1)</p>	<p>Example 471 99%, 3.42 432(M + 1)</p>	<p>Example 472 99%, 3.347 446(M + 1)</p>
	Rx		
Ry			
	<p>Example 473 98%, 3.36 449(M + 1)</p>	<p>Example 474 91%, 3.634 468(M + 1)</p>	<p>Example 475 97%, 3.503 454(M + 1)</p>

TABLE 4-2-continued

basic structure					
$\text{Rx} \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \\ \text{O} \end{array} \text{Ry}$					
Ry	<table border="1"> <thead> <tr> <th colspan="2">Rx</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>	Rx			
Rx					
					
	<table border="1"> <tbody> <tr> <td>Example 476 95%, 3.551 480(M + 1)</td> <td>Example 477 99%, 3.369 468(M + 1)</td> </tr> </tbody> </table>	Example 476 95%, 3.551 480(M + 1)	Example 477 99%, 3.369 468(M + 1)		
Example 476 95%, 3.551 480(M + 1)	Example 477 99%, 3.369 468(M + 1)				

upper line: Example No.
middle line: HPLC purity(220 nm), retention time(min)
lower line: MS(APCI+, m/e)

TABLE 4-3

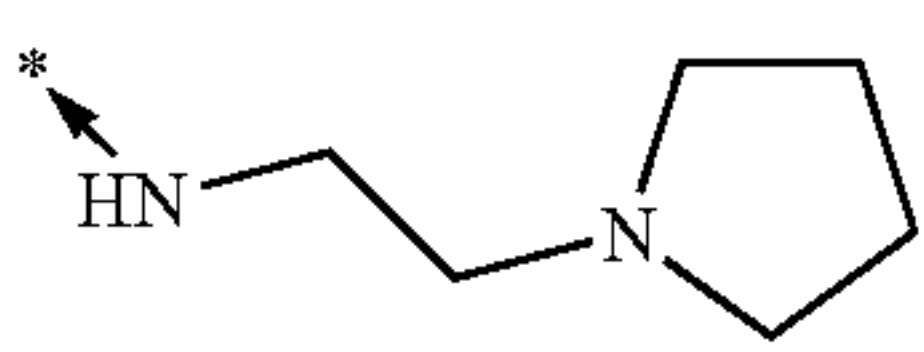
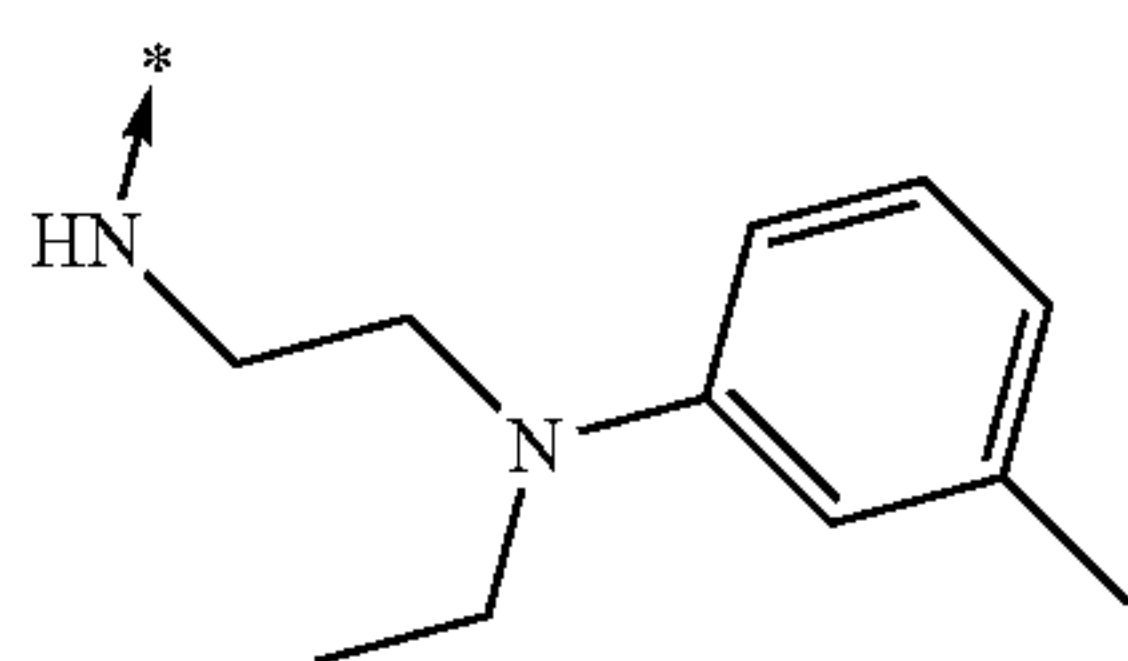
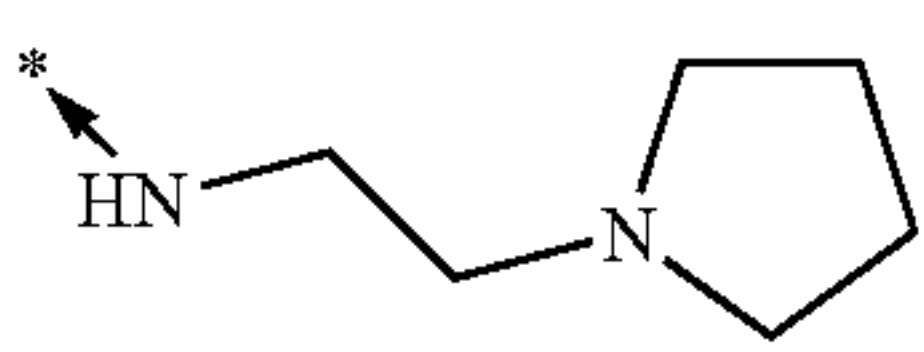
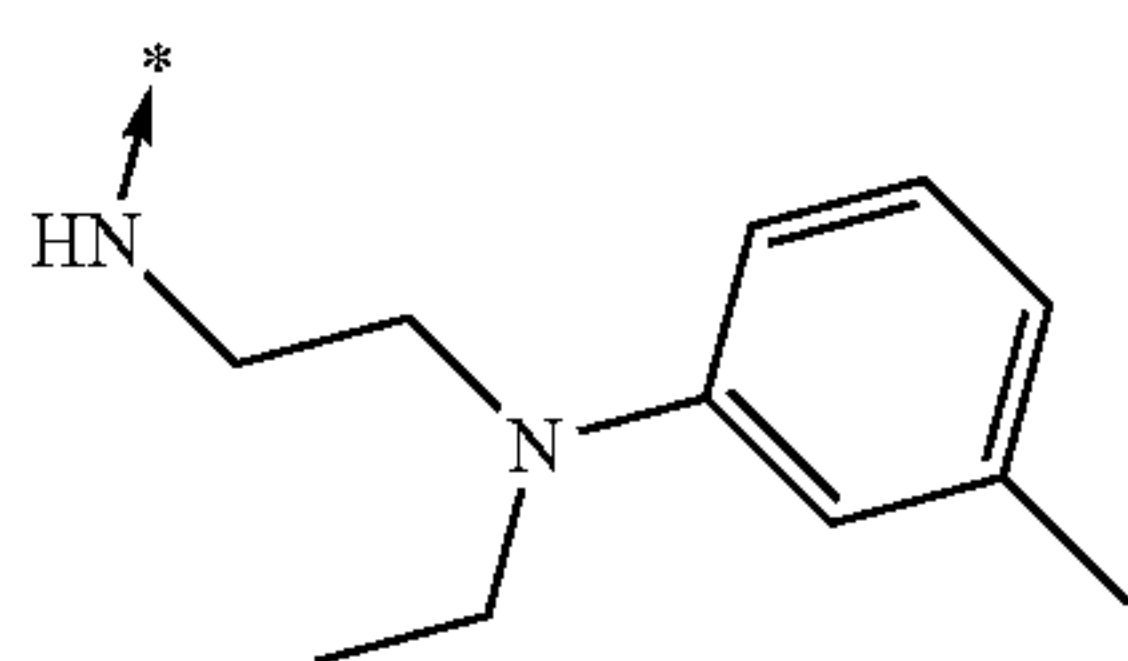
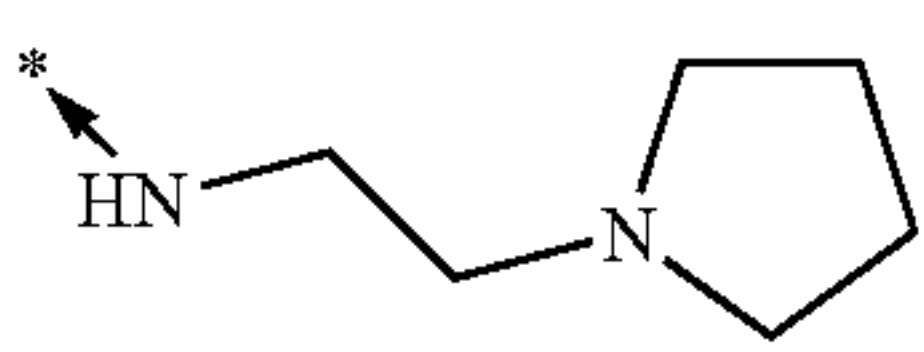
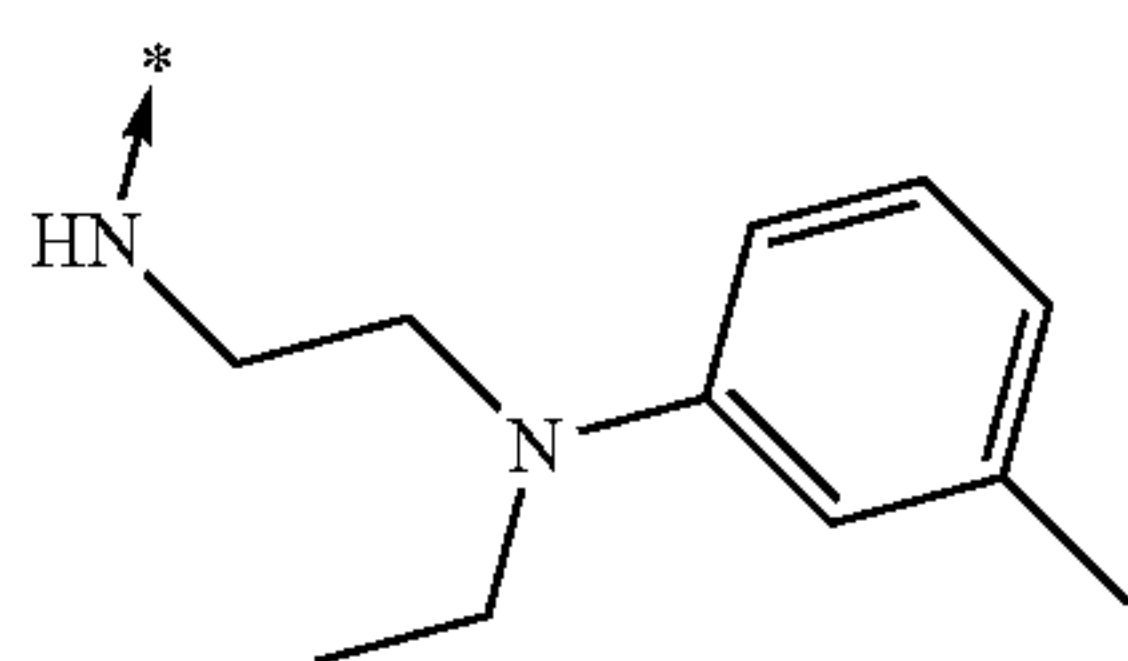
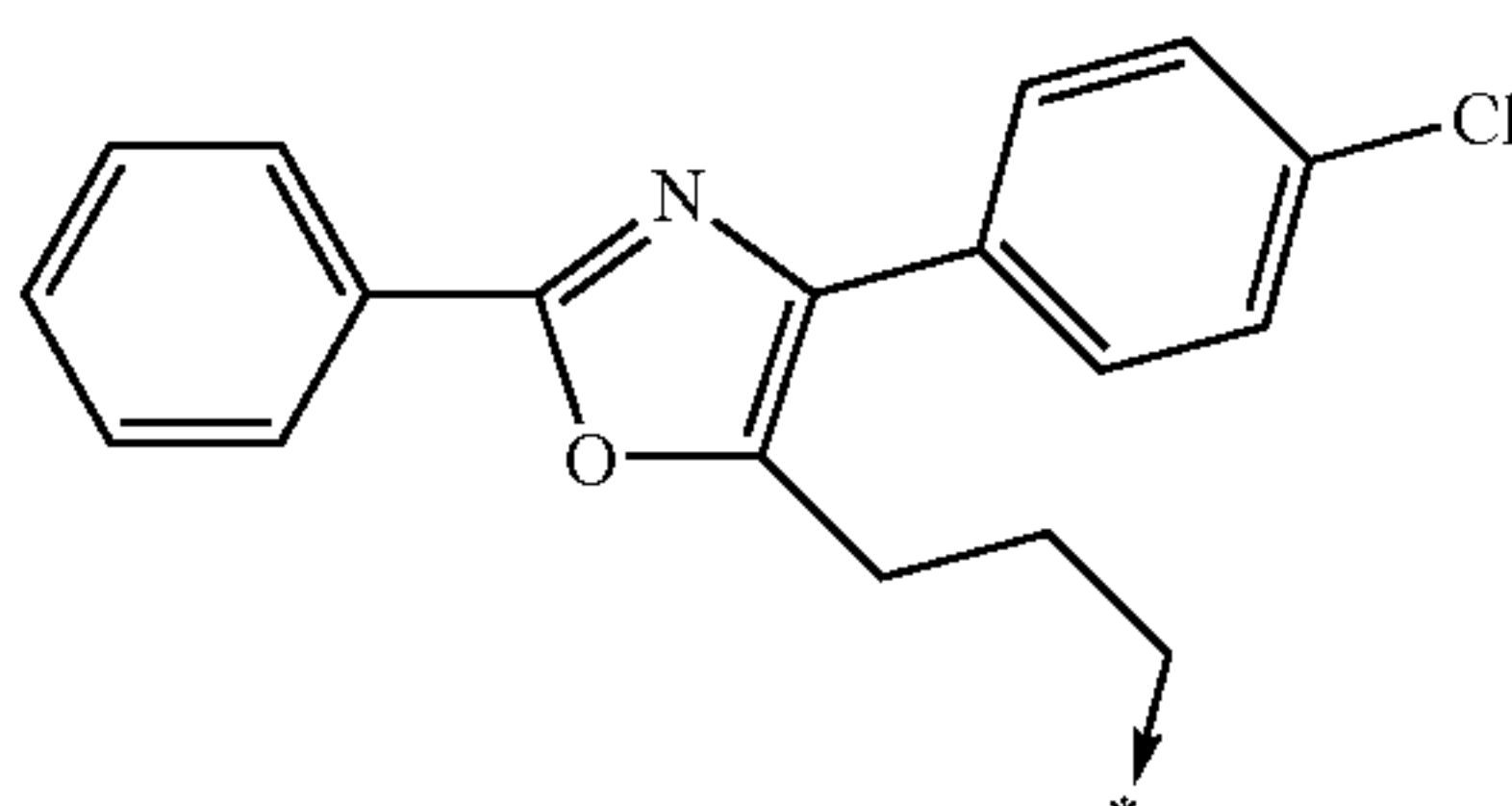
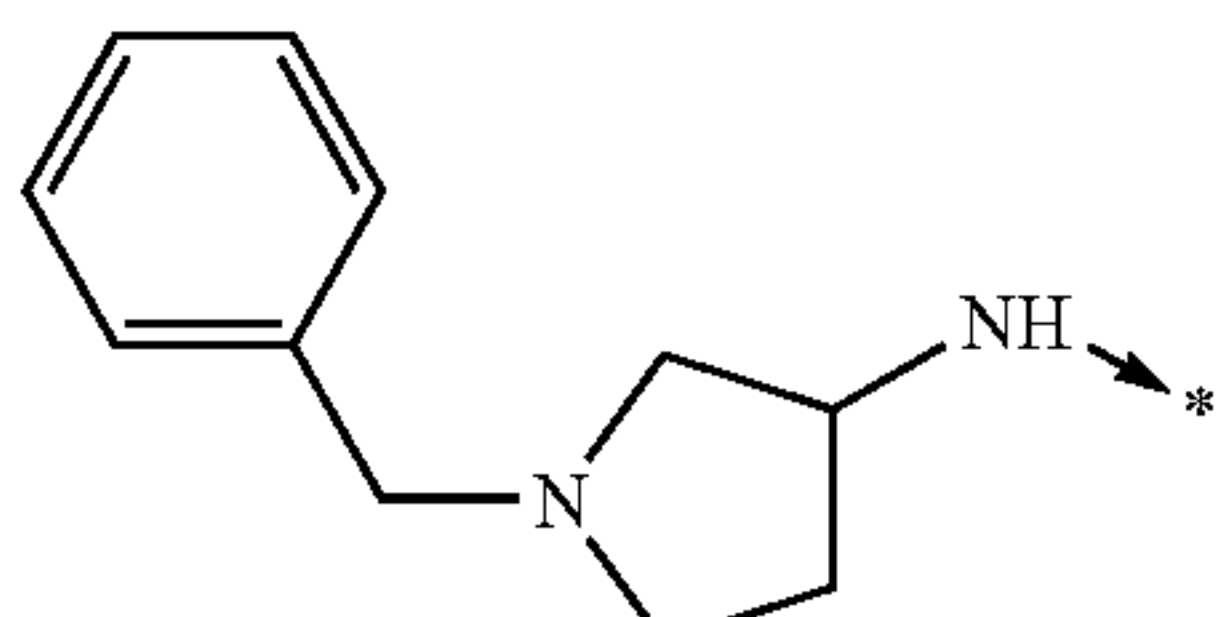
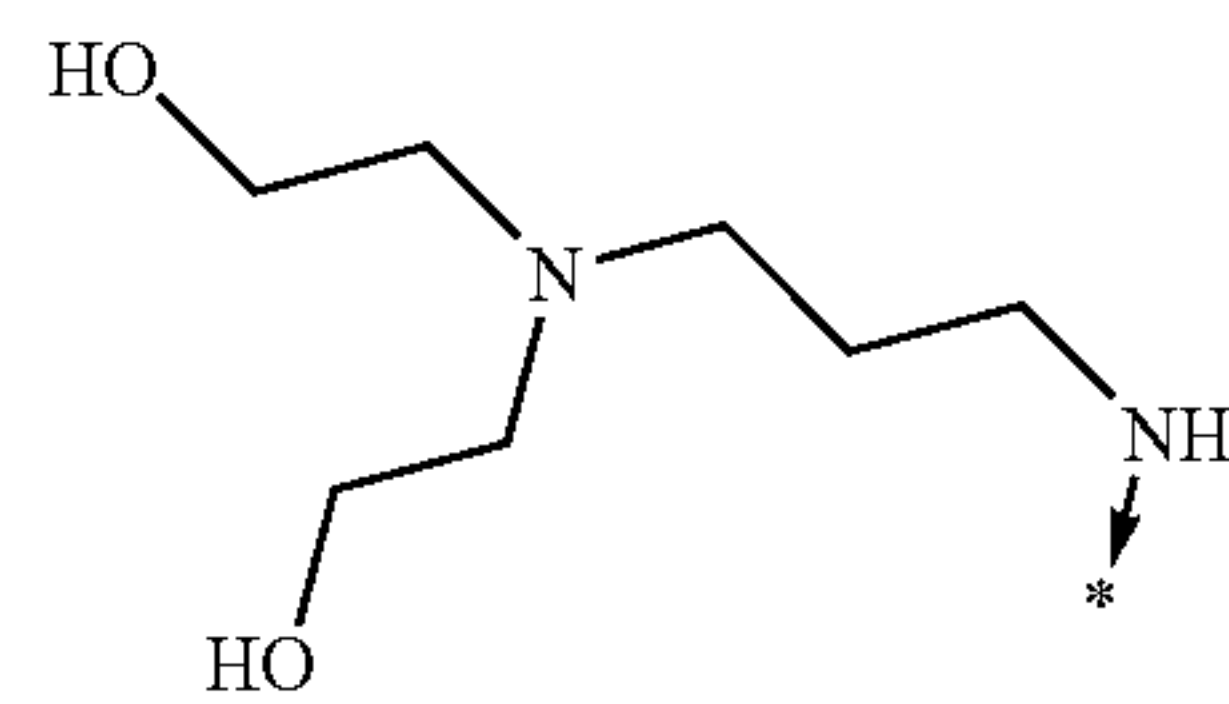
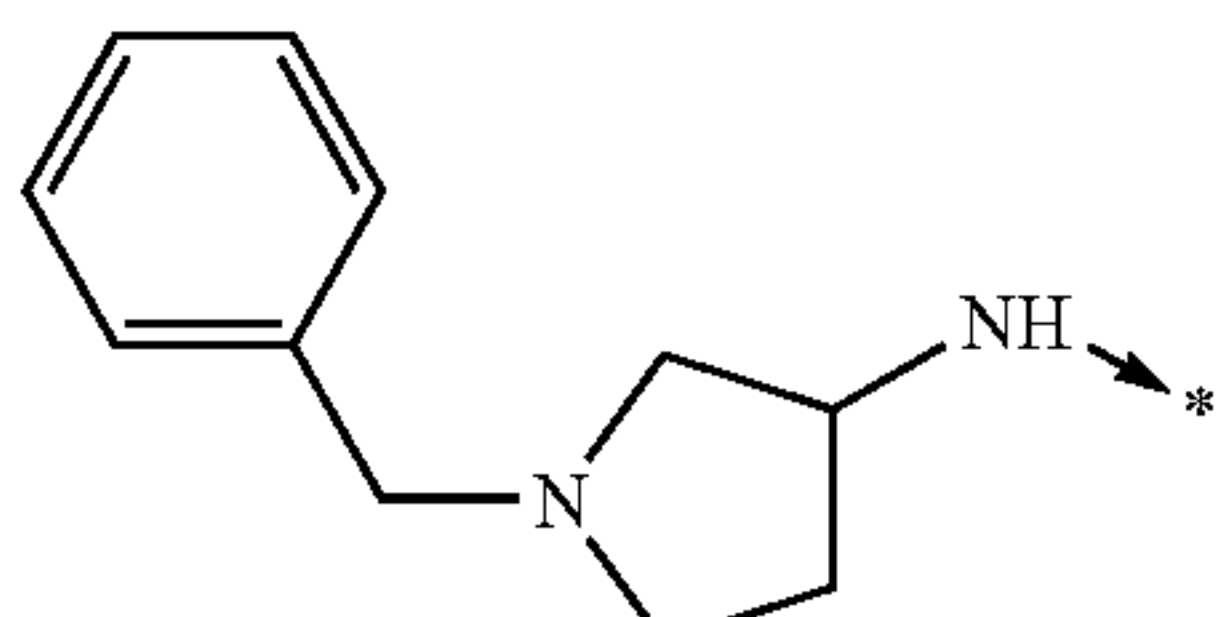
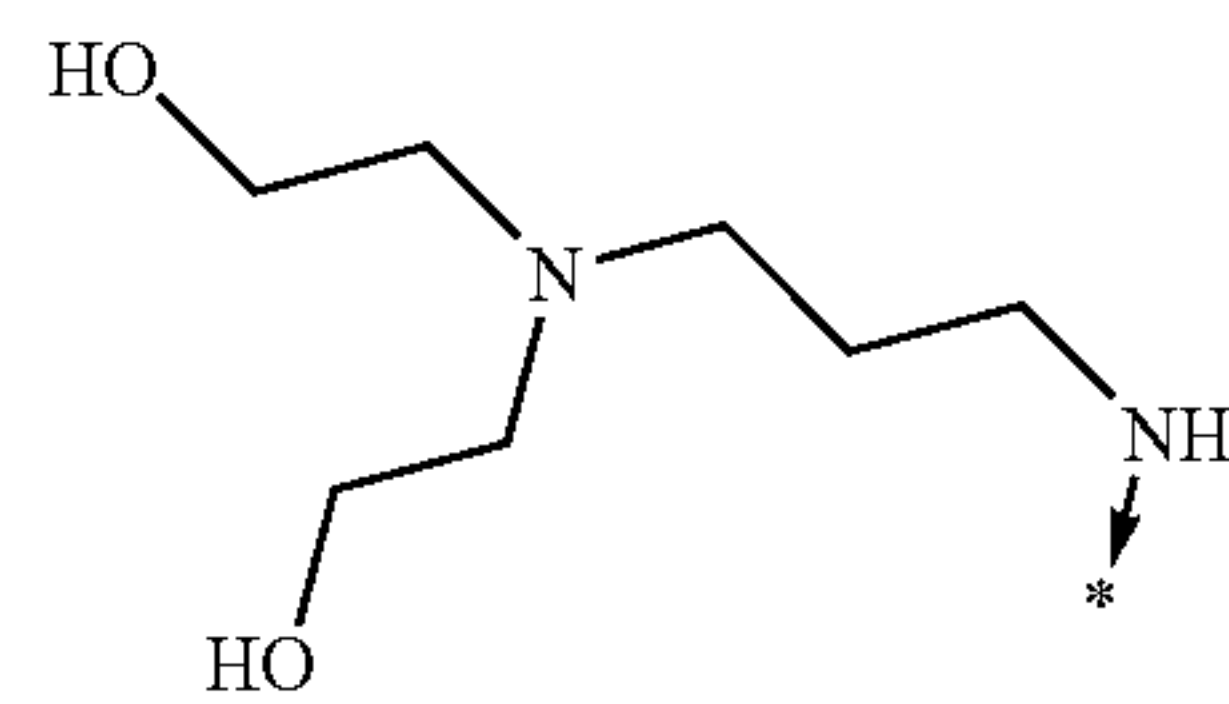
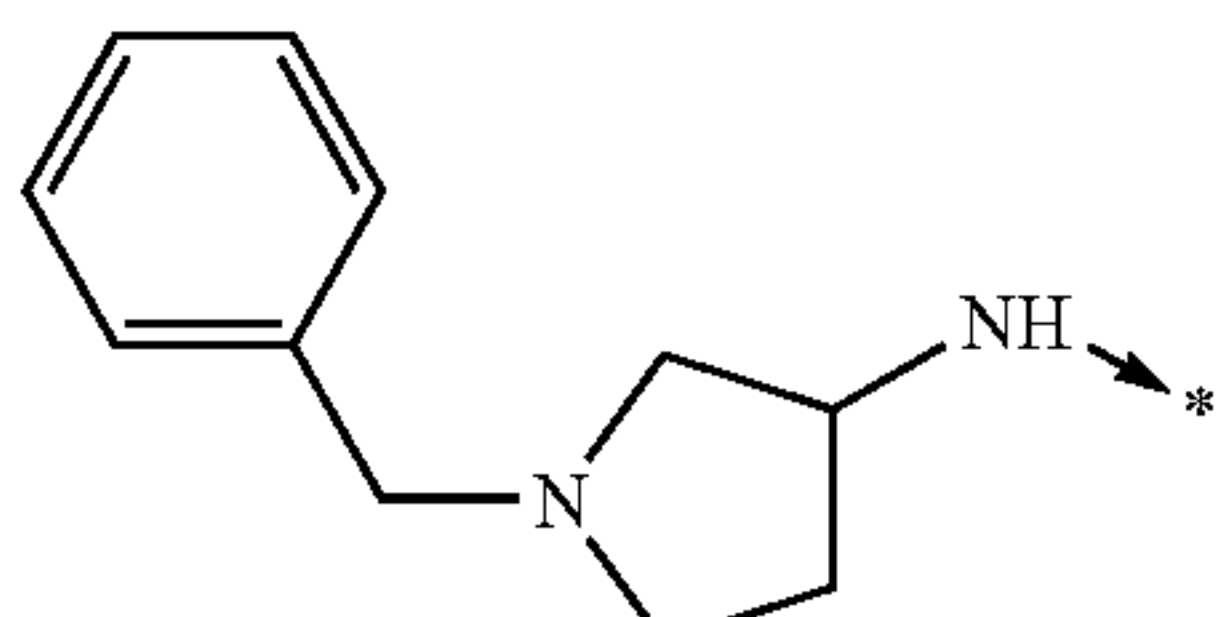
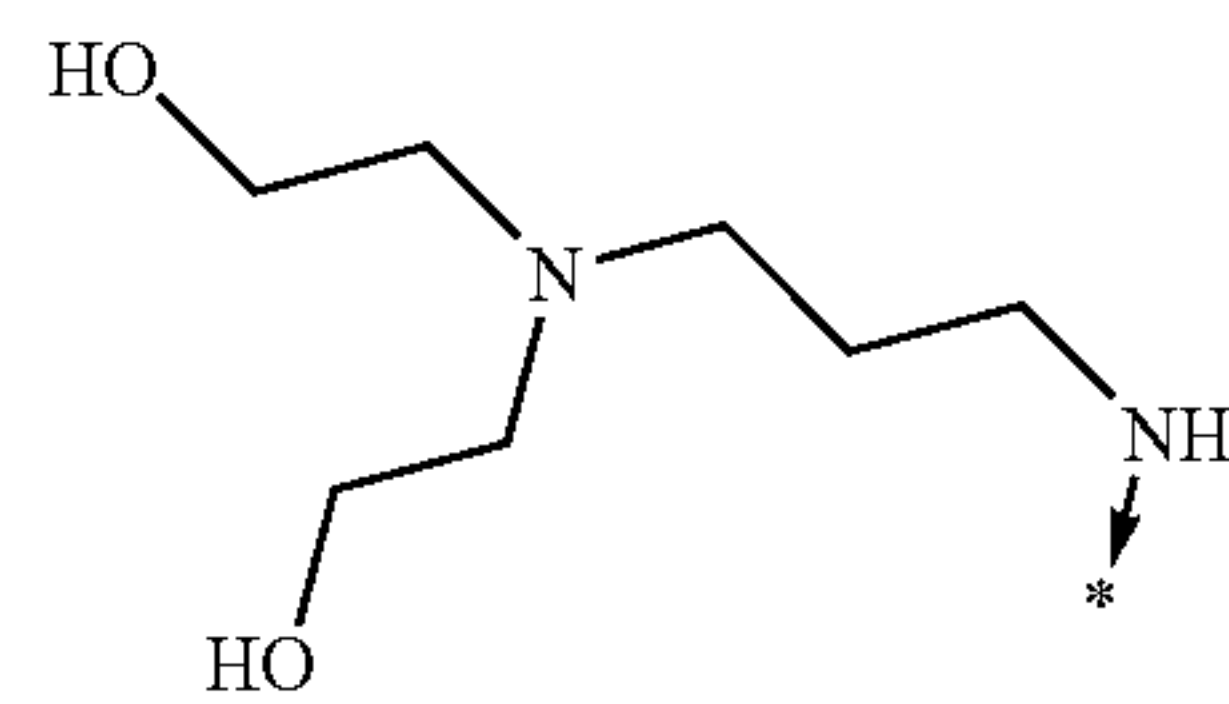
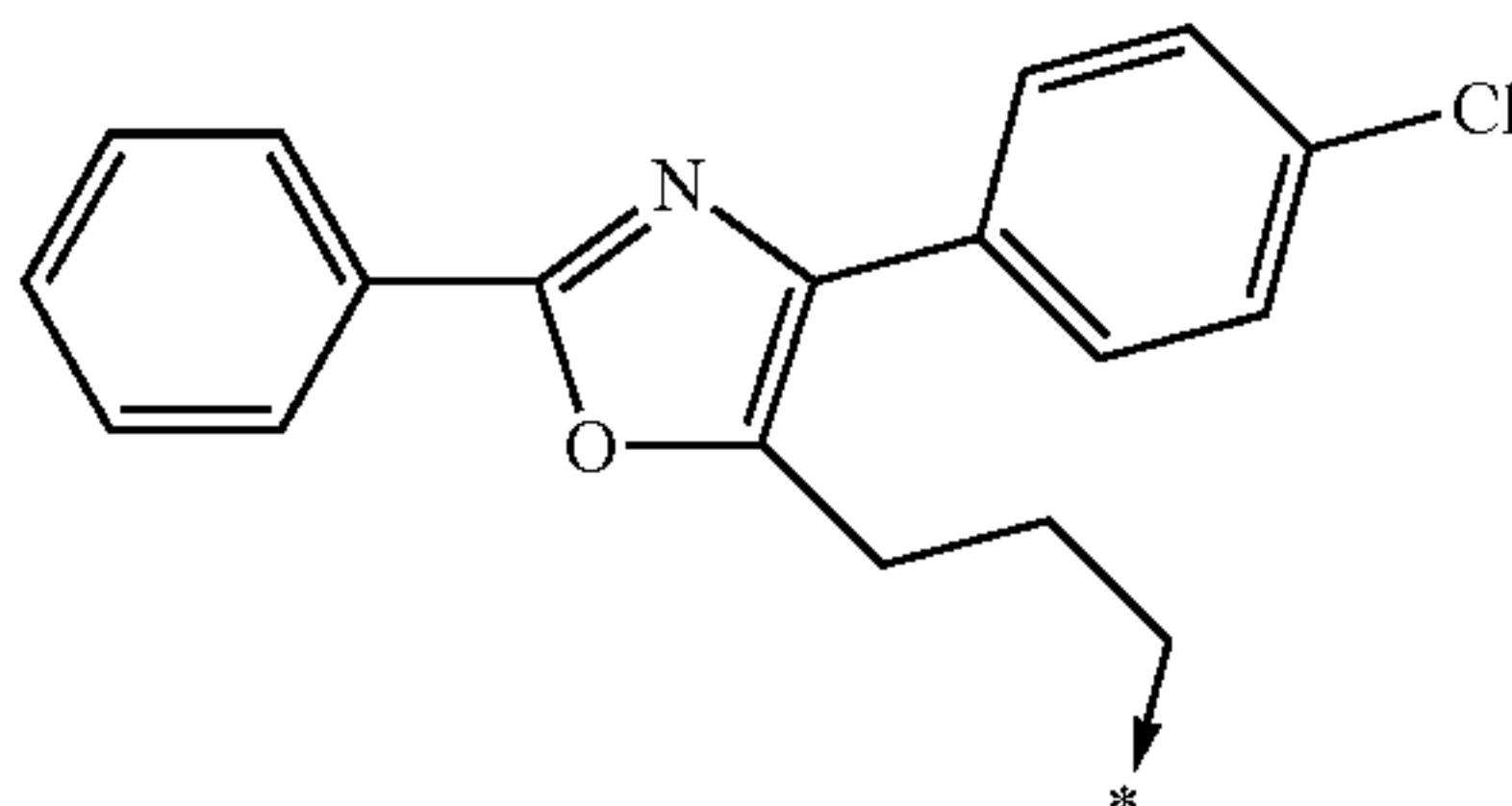
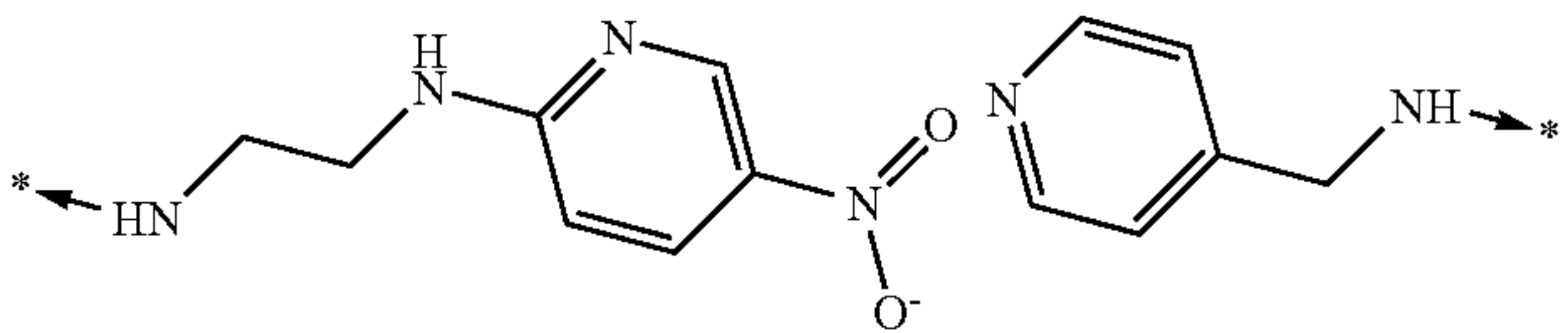
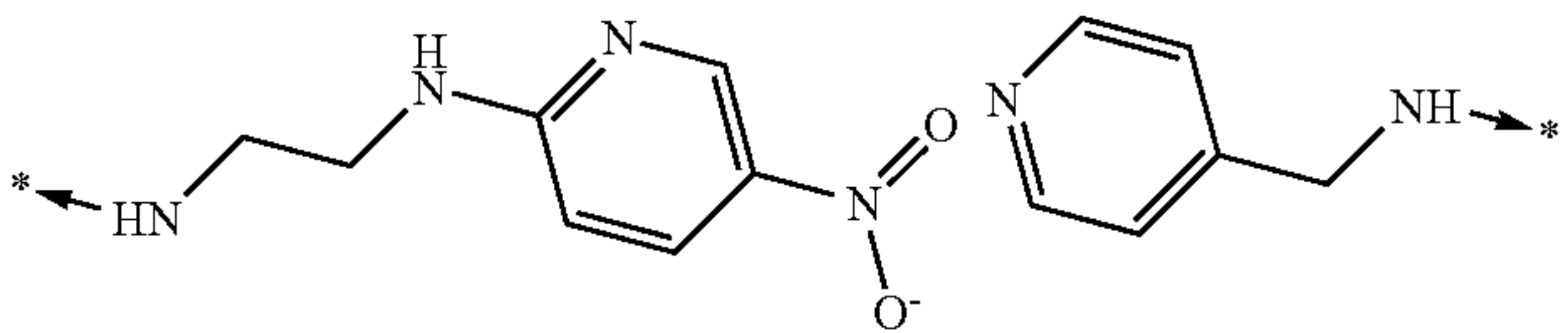
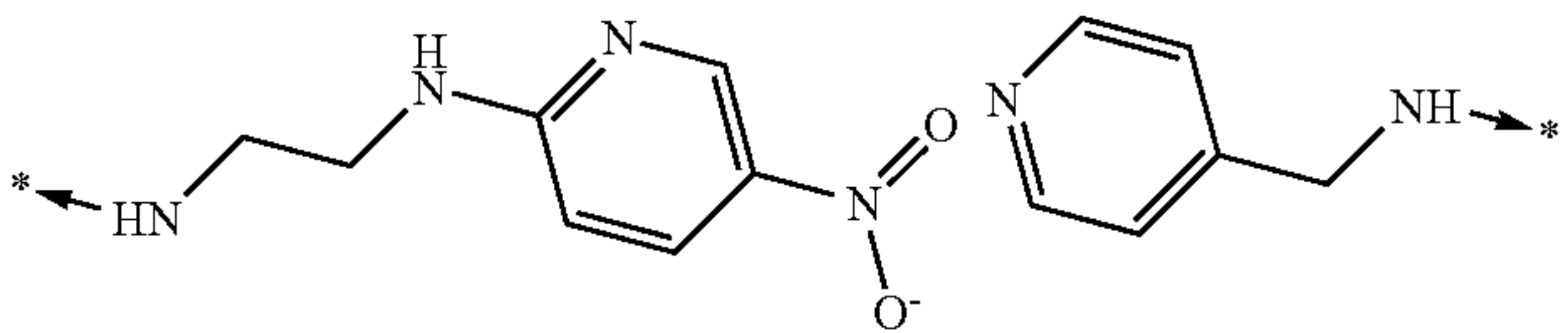
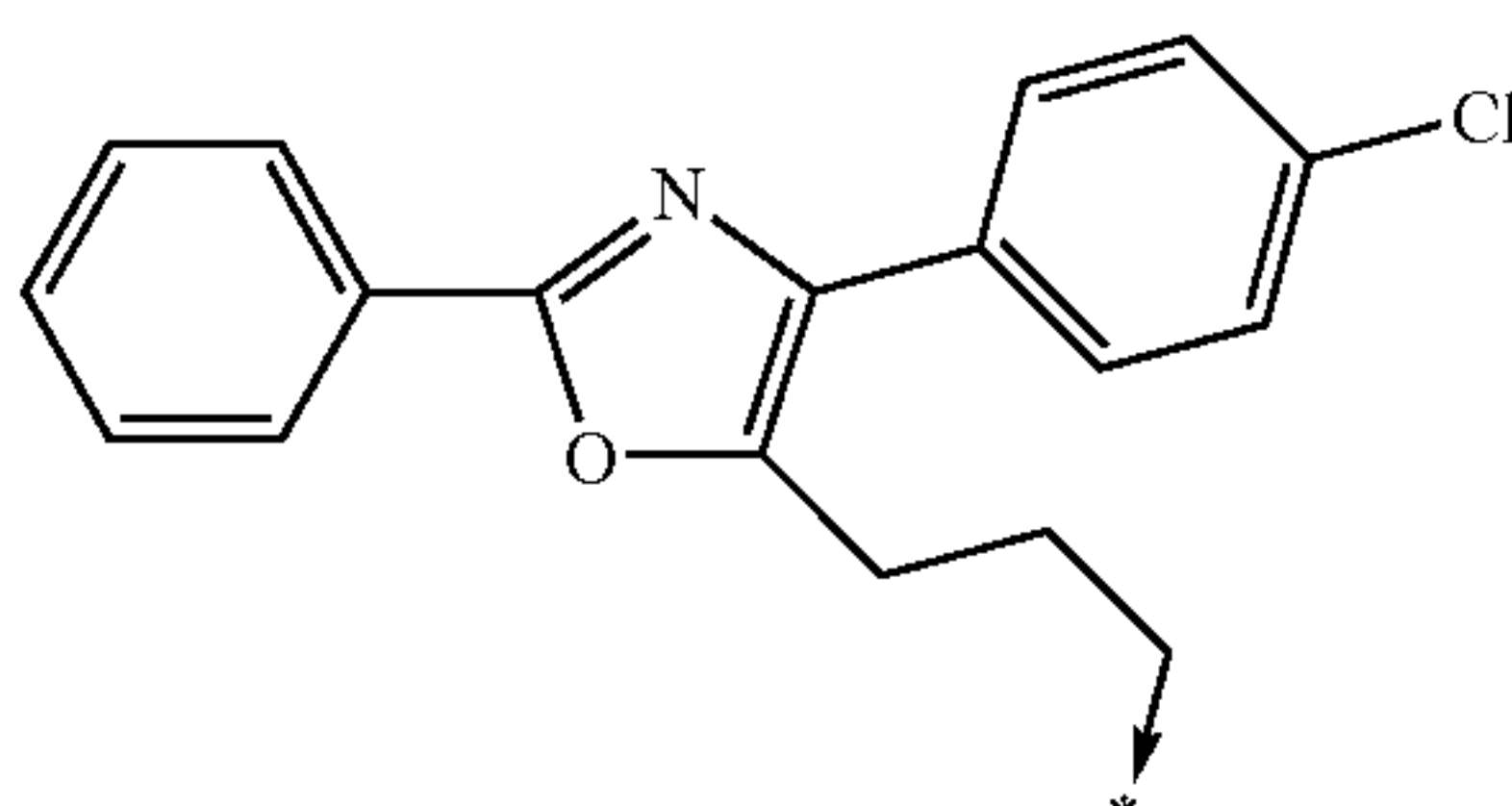
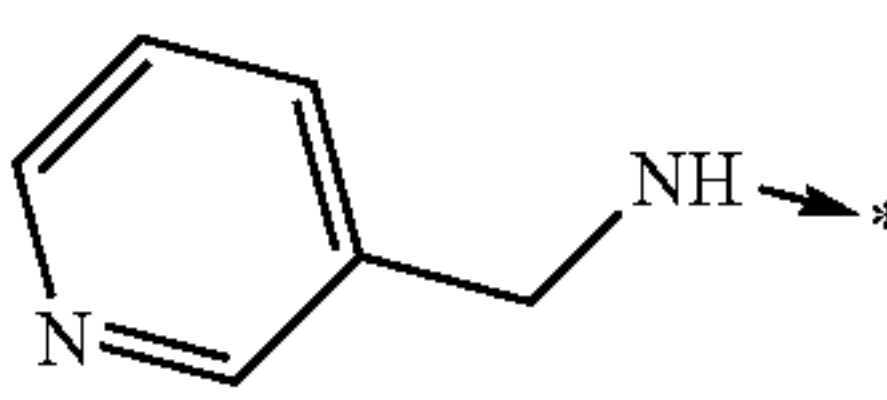
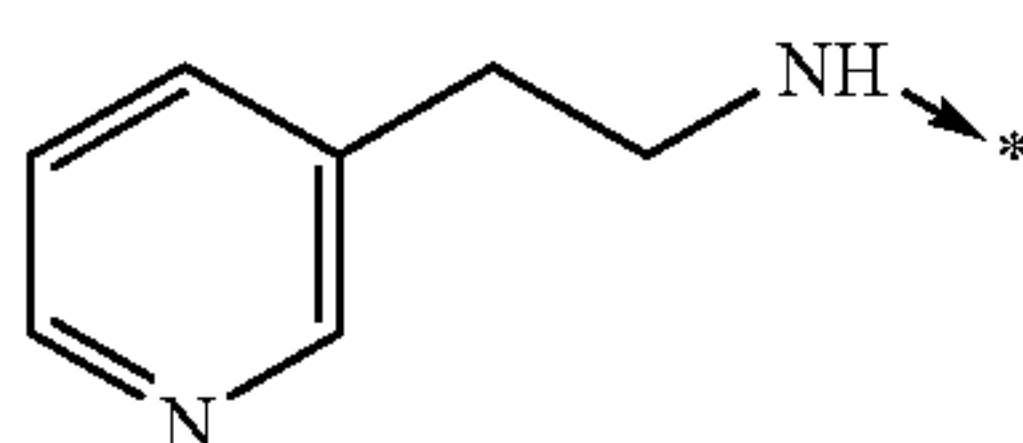
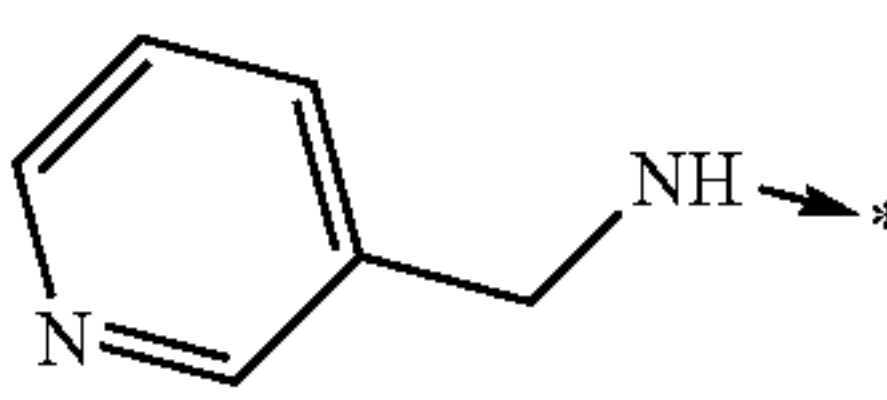
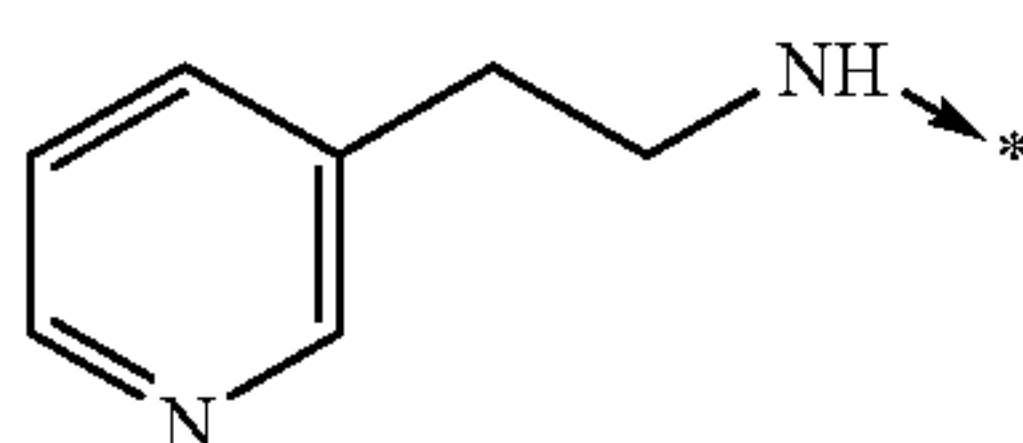
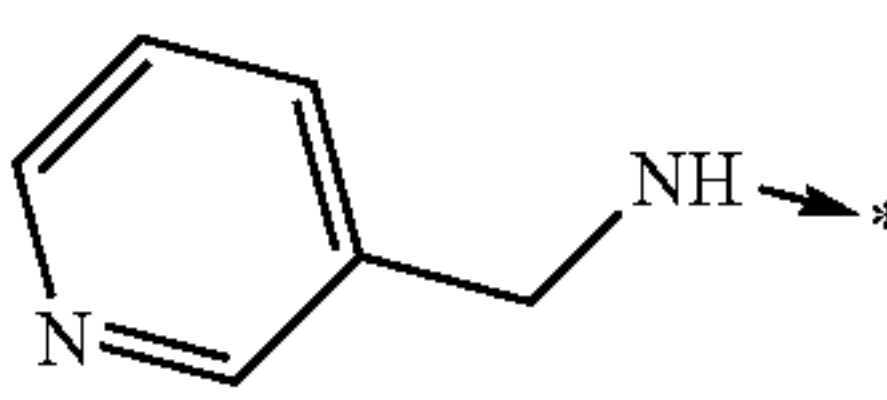
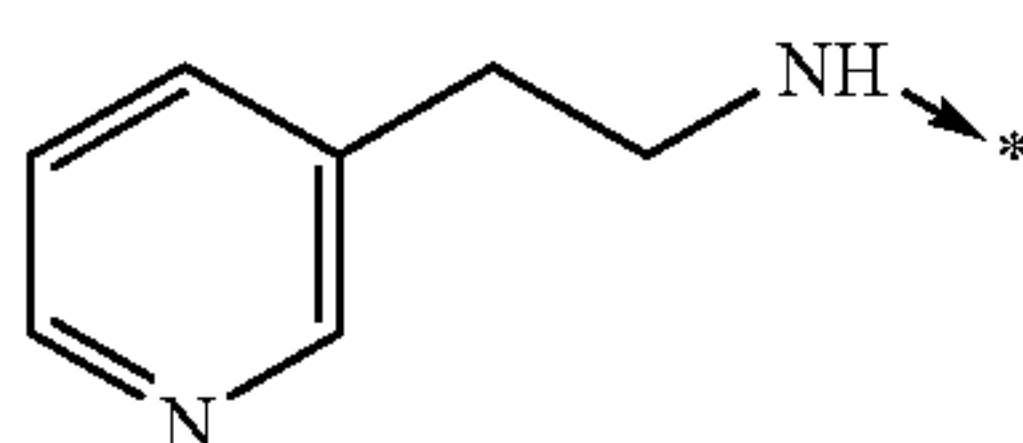
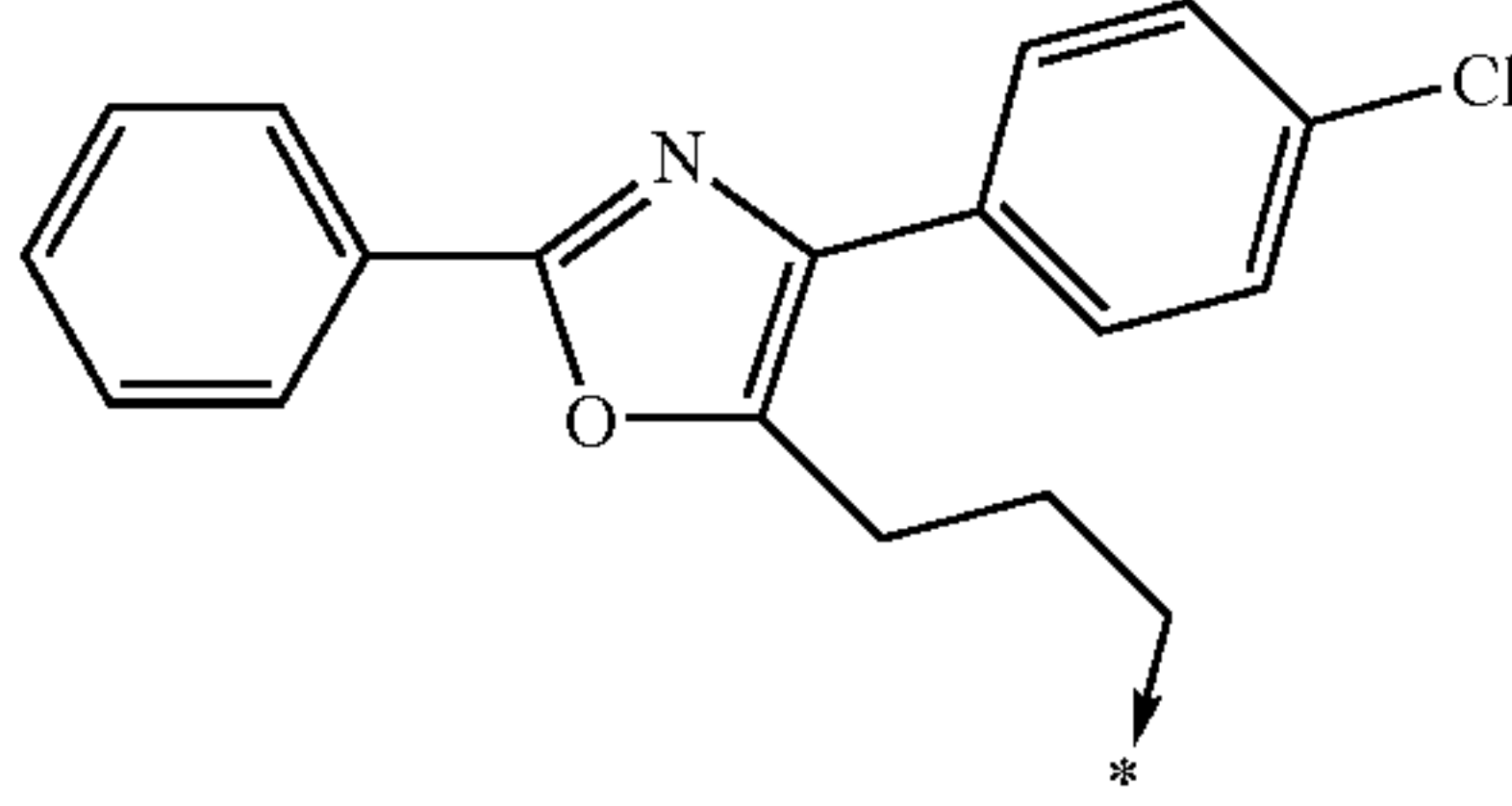
basic structure					
$\text{Rx} \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \\ \text{O} \end{array} \text{Ry}$					
Ry	<table border="1"> <thead> <tr> <th colspan="2">Rx</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>	Rx			
Rx					
					
	<table border="1"> <tbody> <tr> <td>Example 478 99%, 3.426 438(M + 1)</td> <td>Example 479 99%, 3.874 502(M + 1)</td> </tr> </tbody> </table>	Example 478 99%, 3.426 438(M + 1)	Example 479 99%, 3.874 502(M + 1)		
Example 478 99%, 3.426 438(M + 1)	Example 479 99%, 3.874 502(M + 1)				
Ry	<table border="1"> <thead> <tr> <th colspan="2">Rx</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> </tr> </tbody> </table>	Rx			
Rx					
					

TABLE 4-3-continued

basic structure							
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$							
	<table border="0"> <tr> <td>Example 480</td> <td>Example 481</td> </tr> <tr> <td>93%, 3.707</td> <td>98%, 3.271</td> </tr> <tr> <td>500(M + 1)</td> <td>486(M + 1)</td> </tr> </table>	Example 480	Example 481	93%, 3.707	98%, 3.271	500(M + 1)	486(M + 1)
Example 480	Example 481						
93%, 3.707	98%, 3.271						
500(M + 1)	486(M + 1)						
Ry	<table border="0"> <tr> <td colspan="2" style="text-align: center;">Rx</td> </tr> <tr> <td colspan="2" style="text-align: center;">  </td> </tr> </table>	Rx					
Rx							
							
	<table border="0"> <tr> <td>Example 482</td> <td>Example 483</td> </tr> <tr> <td>86%, 4.42</td> <td>99%, 3.374</td> </tr> <tr> <td>506(M + 1)</td> <td>432(M + 1)</td> </tr> </table>	Example 482	Example 483	86%, 4.42	99%, 3.374	506(M + 1)	432(M + 1)
Example 482	Example 483						
86%, 4.42	99%, 3.374						
506(M + 1)	432(M + 1)						
Ry	<table border="0"> <tr> <td colspan="2" style="text-align: center;">Rx</td> </tr> <tr> <td style="text-align: center;">  </td> <td style="text-align: center;">  </td> </tr> </table>	Rx					
Rx							
							
	<table border="0"> <tr> <td>Example 484</td> <td>Example 485</td> </tr> <tr> <td>100%, 3.378</td> <td>99%, 3.361</td> </tr> <tr> <td>432(M + 1)</td> <td>446(M + 1)</td> </tr> </table>	Example 484	Example 485	100%, 3.378	99%, 3.361	432(M + 1)	446(M + 1)
Example 484	Example 485						
100%, 3.378	99%, 3.361						
432(M + 1)	446(M + 1)						

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

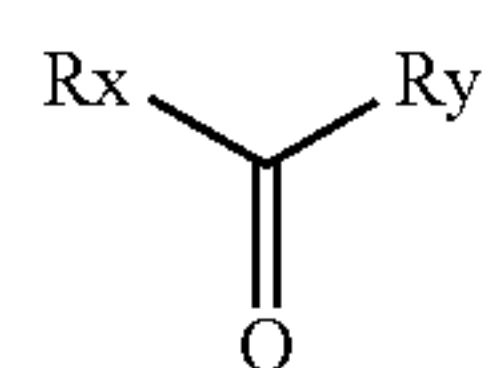
TABLE 4-4

basic structure										
$\begin{array}{c} \text{Rx} \quad \text{Ry} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{O} \end{array}$										
	Rx									
Ry										
	<table border="0"> <tr> <td>Example 486</td> <td>Example 487</td> <td>Example 488</td> </tr> <tr> <td>100%, 4.877</td> <td>100%, 4.844</td> <td>97%, 5.331</td> </tr> <tr> <td>417(M + 1)</td> <td>477(M + 1)</td> <td>507(M + 1)</td> </tr> </table>	Example 486	Example 487	Example 488	100%, 4.877	100%, 4.844	97%, 5.331	417(M + 1)	477(M + 1)	507(M + 1)
Example 486	Example 487	Example 488								
100%, 4.877	100%, 4.844	97%, 5.331								
417(M + 1)	477(M + 1)	507(M + 1)								
	Rx									
Ry										
	<table border="0"> <tr> <td>Example 489</td> <td>Example 490</td> <td>Example 491</td> </tr> <tr> <td>99%, 5.308</td> <td>99%, 3.534</td> <td>100%, 3.628</td> </tr> <tr> <td>493(M + 1)</td> <td>418(M + 1)</td> <td>468(M + 1)</td> </tr> </table>	Example 489	Example 490	Example 491	99%, 5.308	99%, 3.534	100%, 3.628	493(M + 1)	418(M + 1)	468(M + 1)
Example 489	Example 490	Example 491								
99%, 5.308	99%, 3.534	100%, 3.628								
493(M + 1)	418(M + 1)	468(M + 1)								
	Rx									
Ry										
	<table border="0"> <tr> <td>Example 492</td> <td>Example 493</td> </tr> <tr> <td>95%, 5.026</td> <td>96%, 4.923</td> </tr> <tr> <td>474(M + 1)</td> <td>435(M + 1)</td> </tr> </table>	Example 492	Example 493	95%, 5.026	96%, 4.923	474(M + 1)	435(M + 1)			
Example 492	Example 493									
95%, 5.026	96%, 4.923									
474(M + 1)	435(M + 1)									

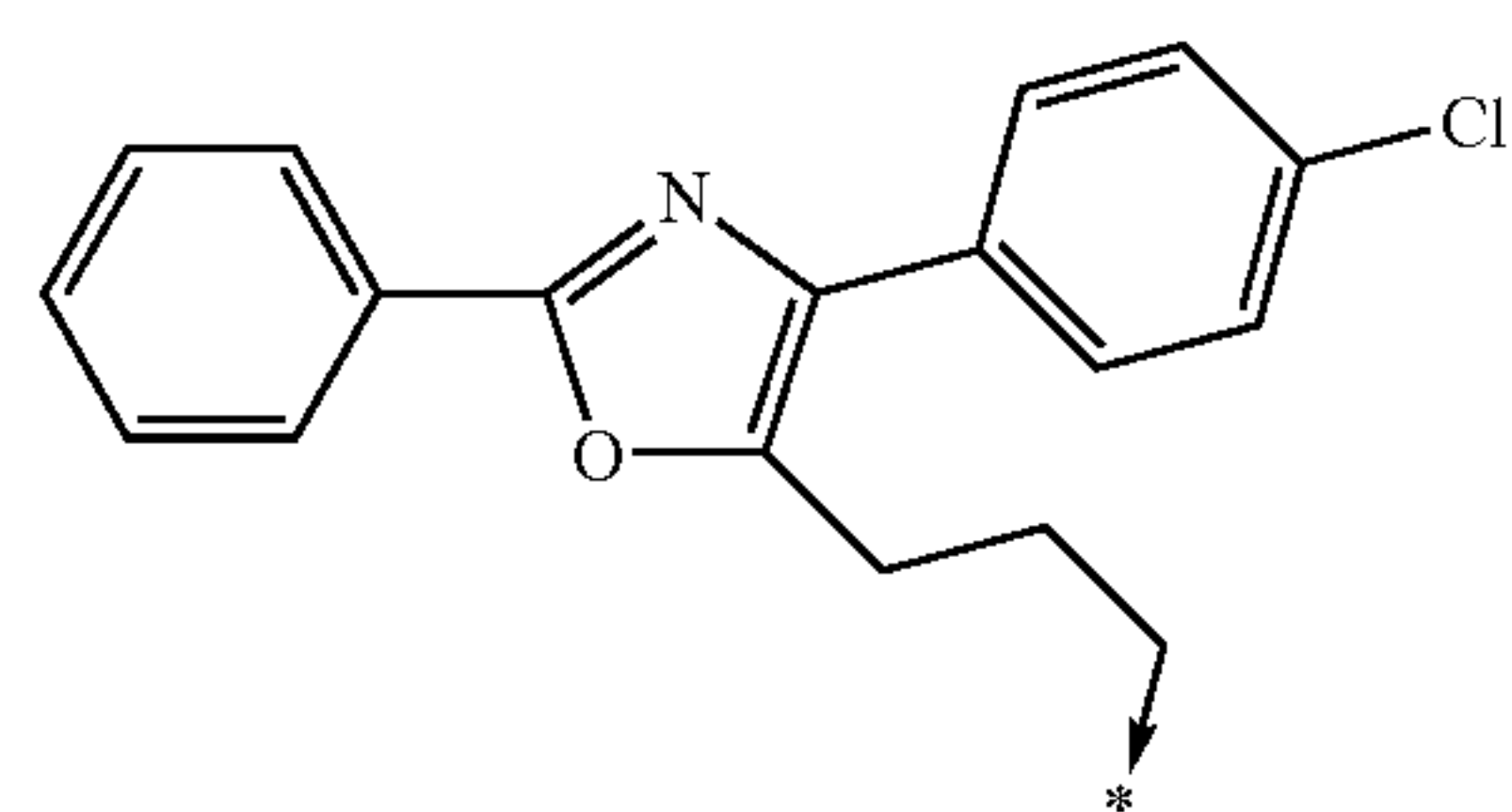
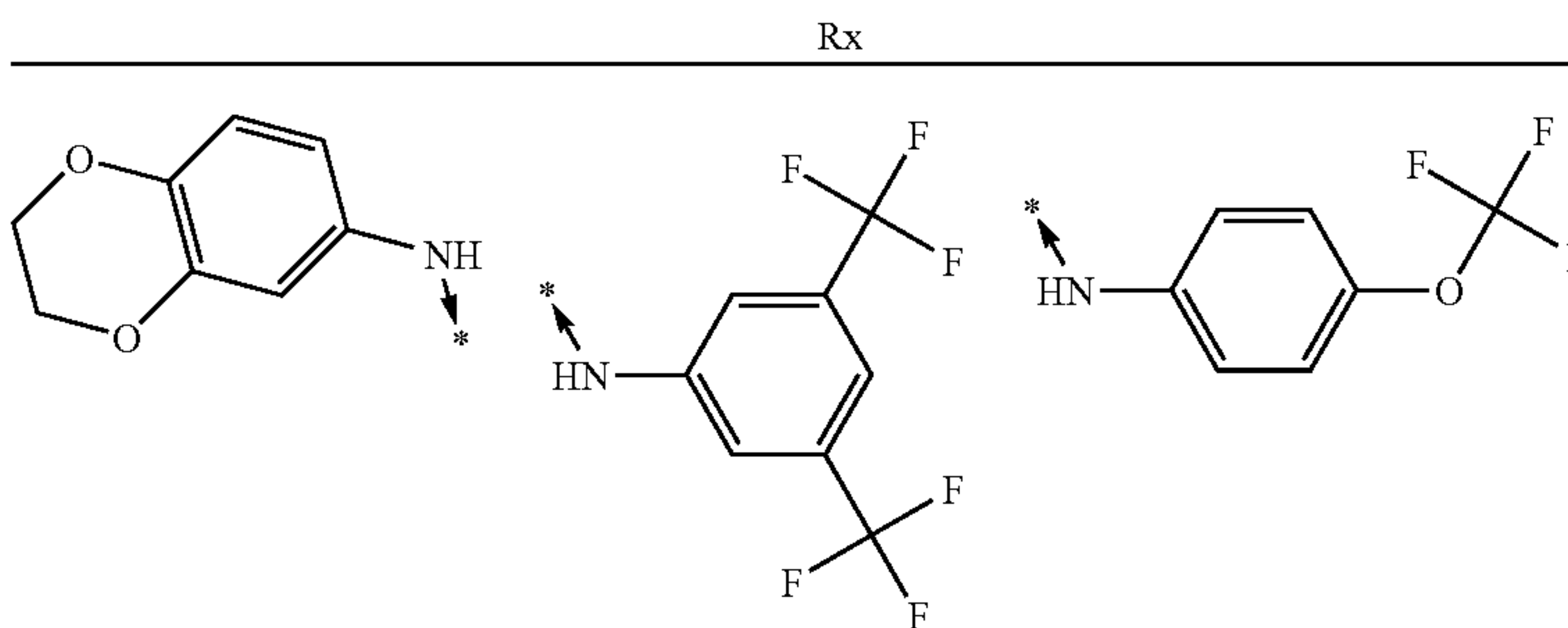
upper line: Example No.
middle line: HPLC purity(220 nm), retention time(min)
lower line: MS(APCI+, m/e)

TABLE 4-5

basic structure



Ry

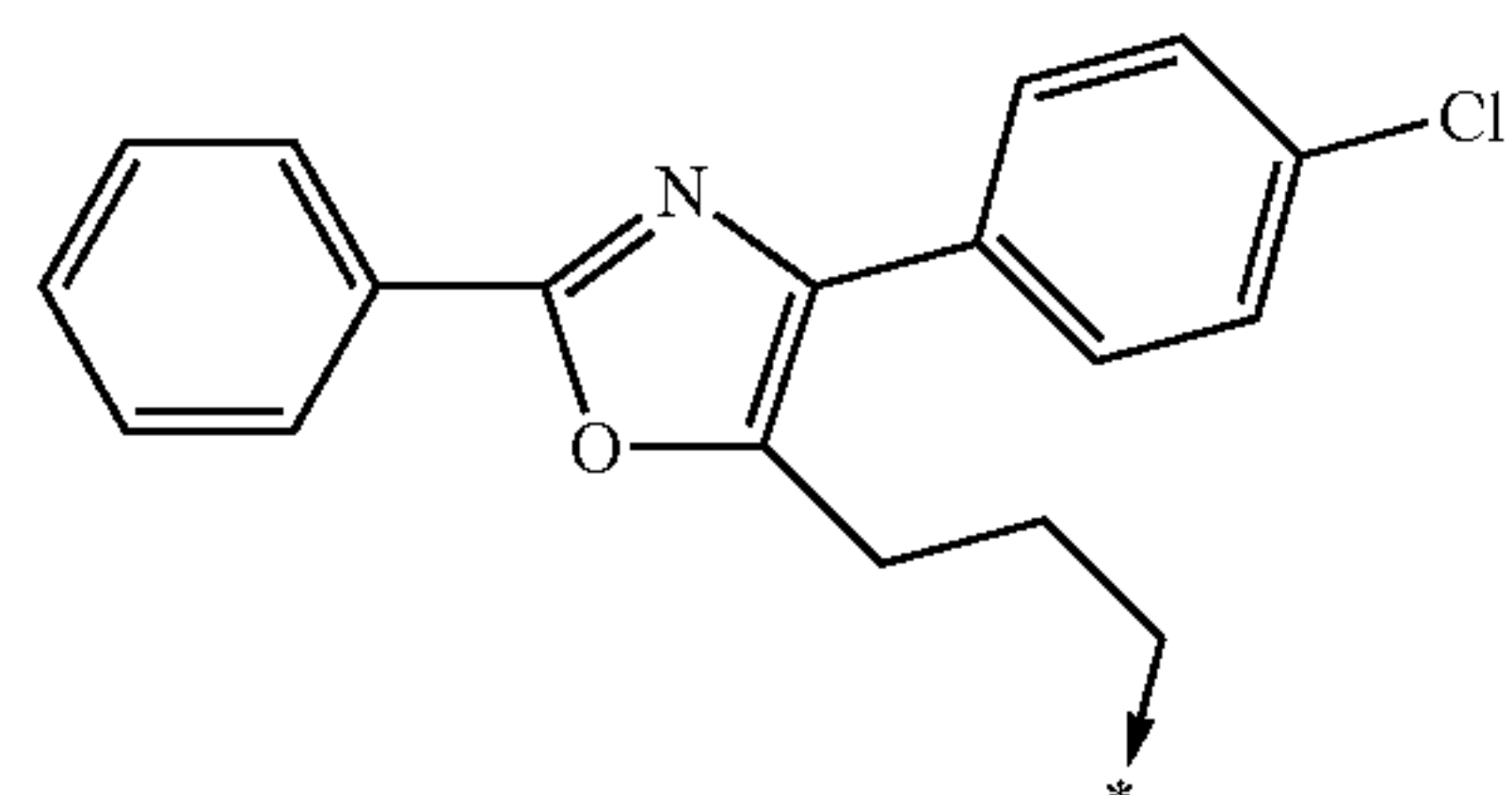
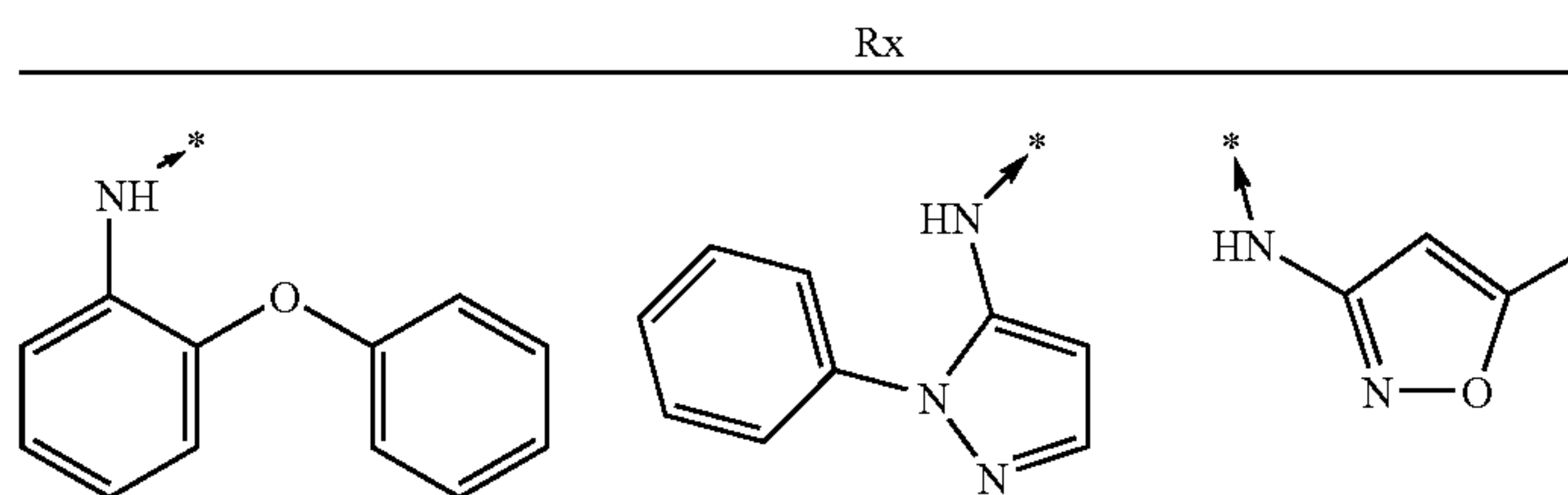


Example 494
98%, 4.707
475(M + 1)

Example 495
95%, 5.488
553(M + 1)

Example 496
100%, 5.216
501(M + 1)

Ry

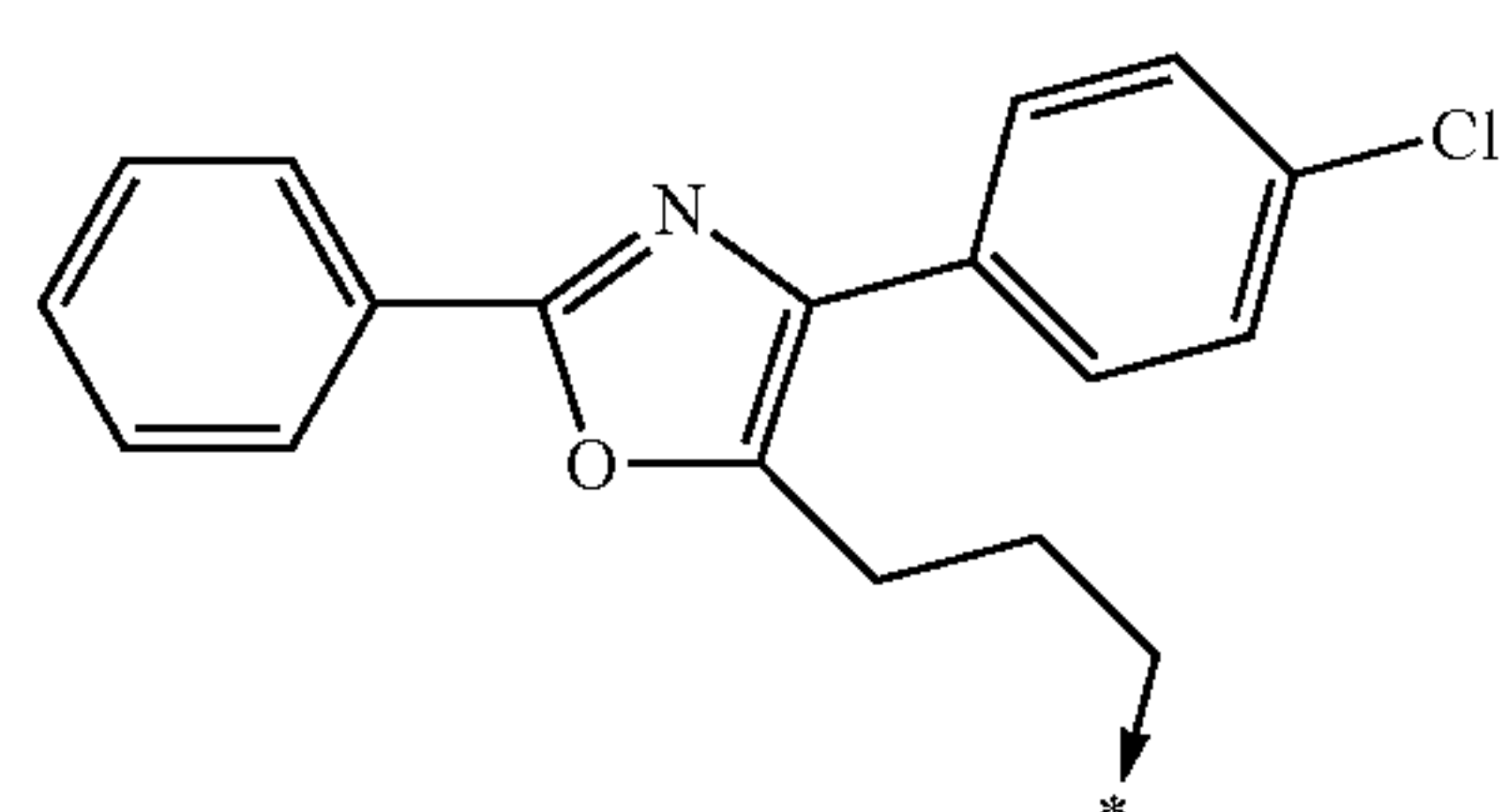
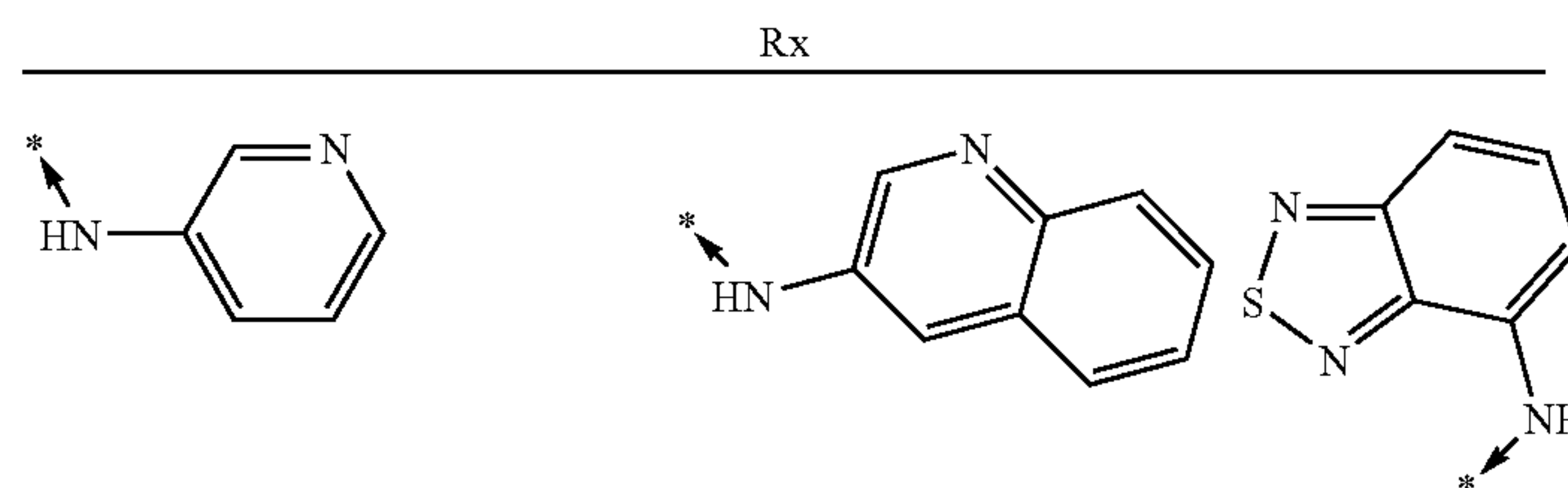


Example 497
100%, 5.355
509(M + 1)

Example 498
90%, 4.623
483(M + 1)

Example 499
88%, 4.611
422(M + 1)

Ry

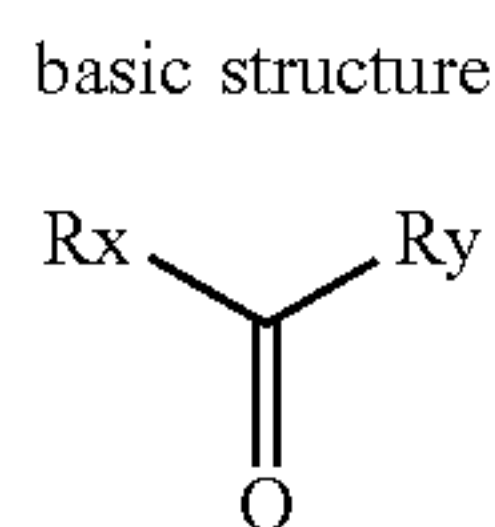


Example 500
99%, 3.479
418(M + 1)

Example 501
97%, 3.846
468(M + 1)

Example 502
95%, 5.099
475(M + 1)

TABLE 4-5-continued



upper line: Example No.
middle line: HPLC purity(220 nm), retention time(min)
lower line: MS(APCI+, m/e)

Example 503

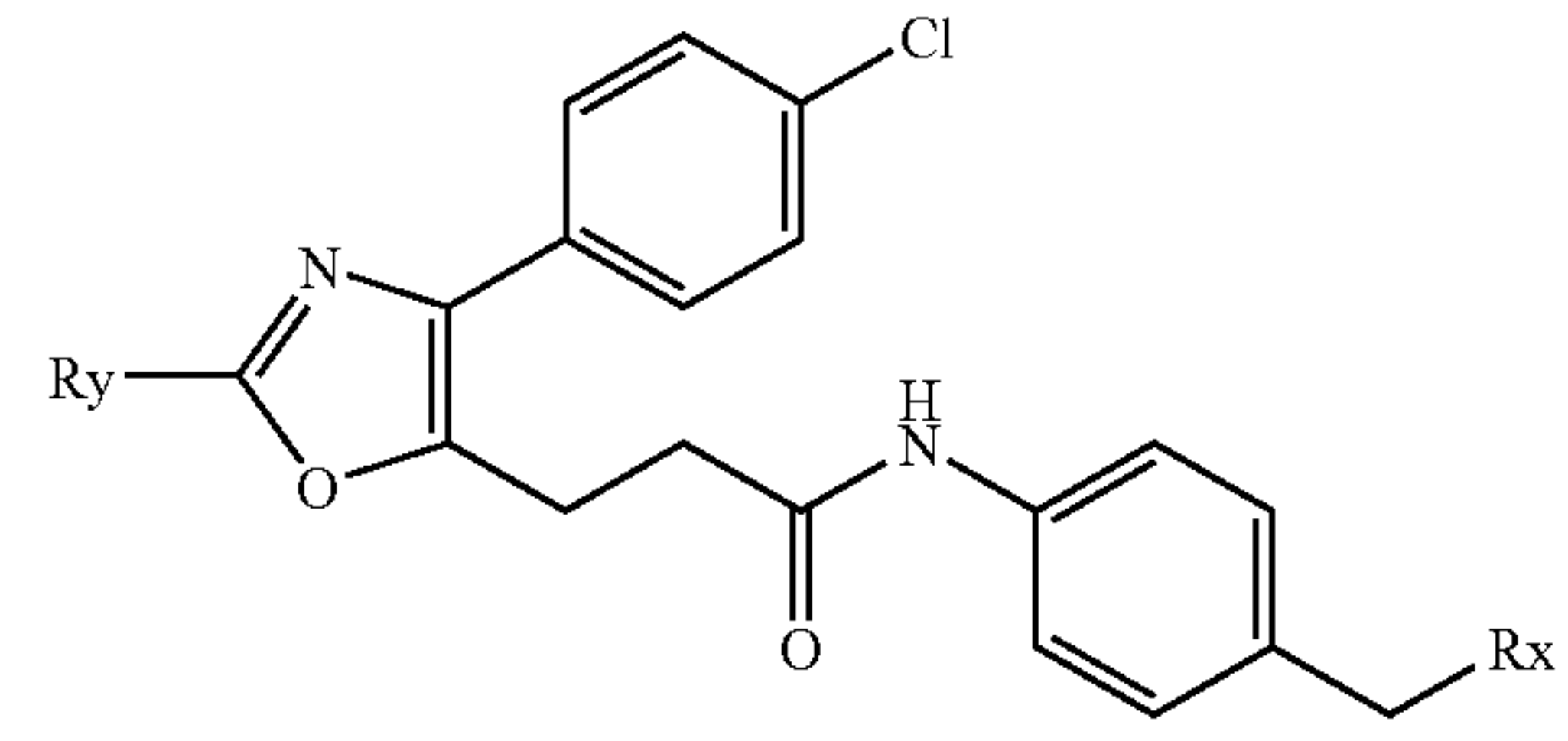
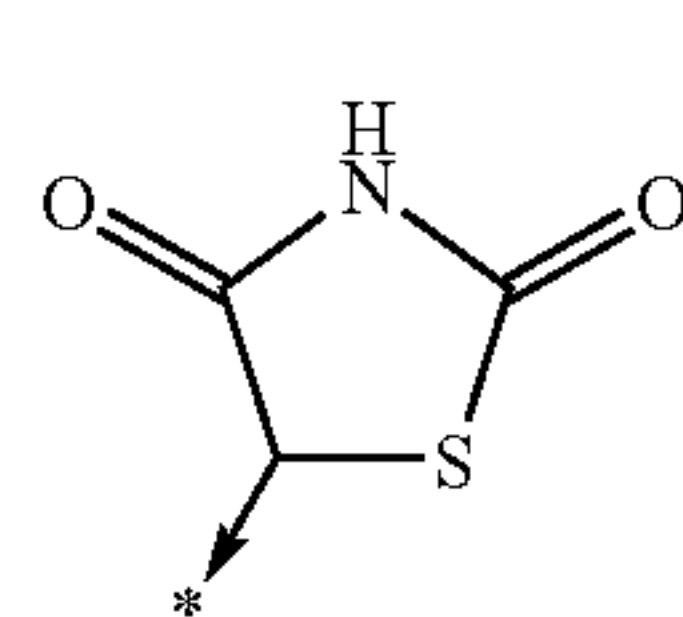
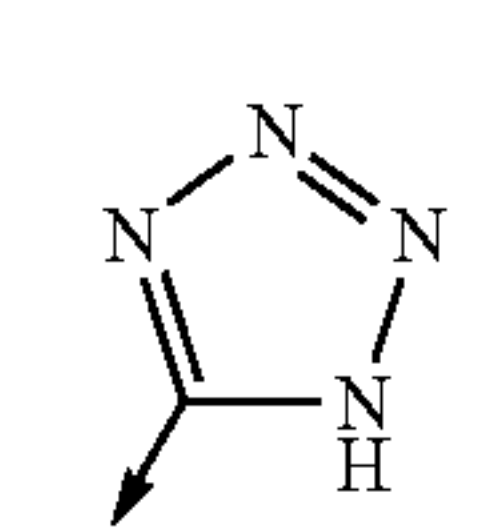
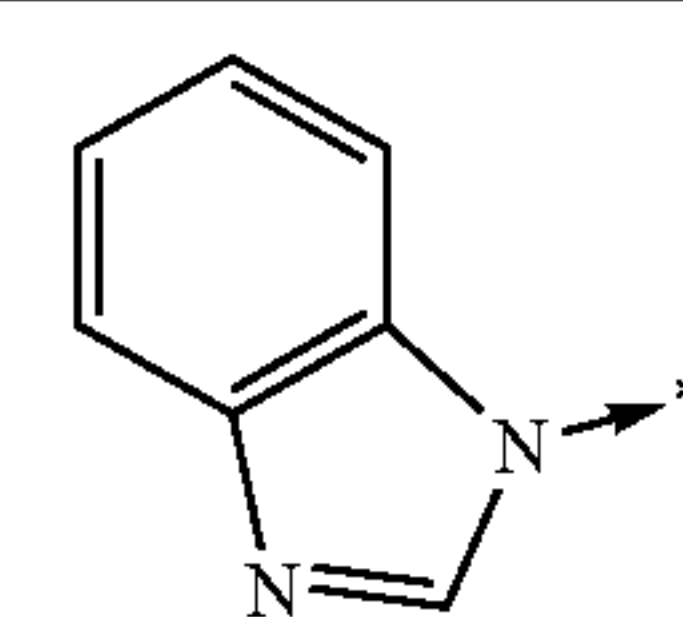
A mixture of 2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolepropionic acid (37 mg), 4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]aniline (35 mg), 1-hydroxy-7-azabenzotriazole (20 mg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (20 mg) and N,N-dimethylformamide (1 ml) was shaken at room temperature for 8 hrs. The reaction mixture was directly poured into preparative HPLC and purified to give the object compound.

Examples 504–508

In the same manner as in Example 503, the object compounds were obtained.

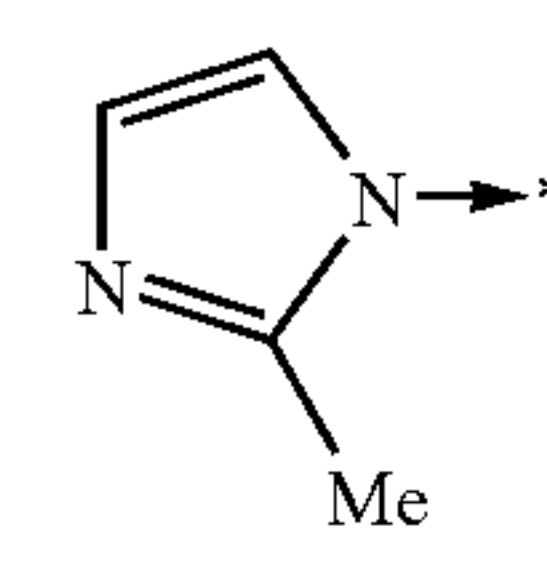
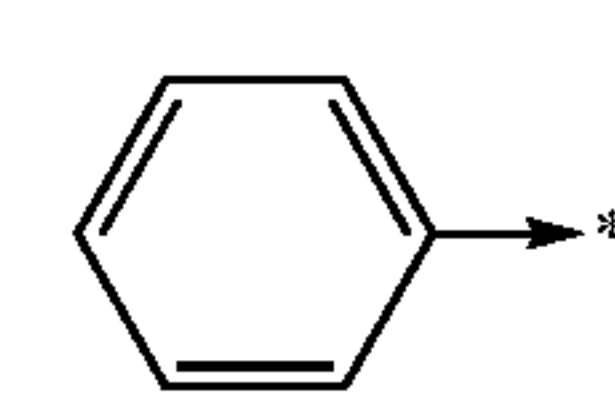
The structure and purity of the object compounds of Examples 503–508 were confirmed by LC-MS, HPLC. The structure, purity (HPLC retention time) and mass spectrum data of the object compounds are shown in [Table 5].

TABLE 5

basic structure		
		
	Rx	
Ry		
	Example 503 100%, 4.278 572(M + 1)	Example 504 99%, 3.998 525(M + 1)

15

TABLE 5-continued

20		Example 505 98%, 3.299 536(M + 1)	Example 506 97%, 3.055 489(M + 1)
25			
30		Example 507 100%, 4.647 546(M + 1)	Example 508 99%, 4.315 499(M + 1)

35

upper line: Example No.
middle line: HPLC purity(220 nm), retention time
lower line: MS(APCI+, m/e)

40

45

Examples 509–874

A mixture of carboxylic acid (0.06 mmol), amine (0.06 mmol), PS-carbodiimide resin (0.94 meq/g, 96 mg) manufactured by Argonaut Technologies Inc. and dichloromethane (0.7 ml) was shaken for 20 hrs. using a 96 well plate with Flex Chem filter. The resin was removed by filtration and the filtrate was concentrated. The residue was purified by preparative HPLC to give the object compound.

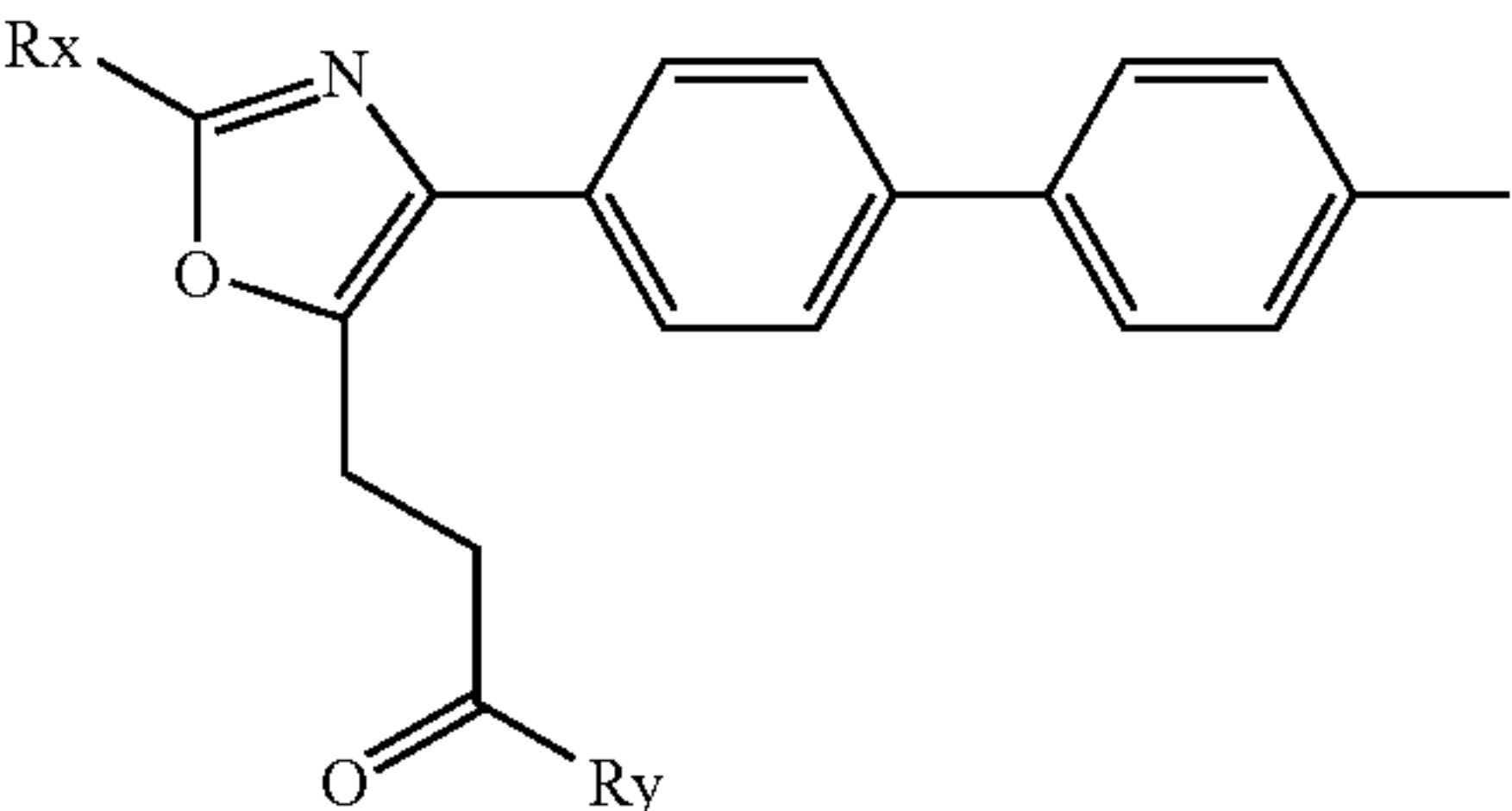

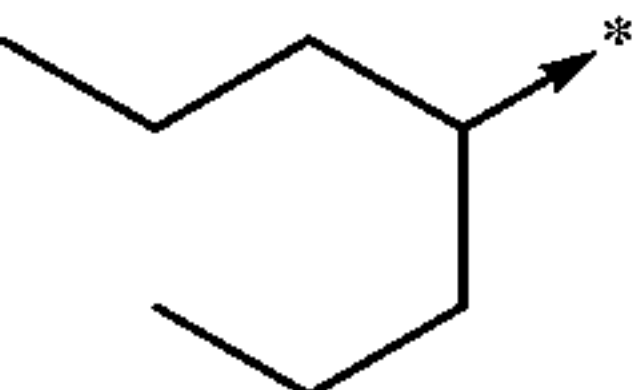
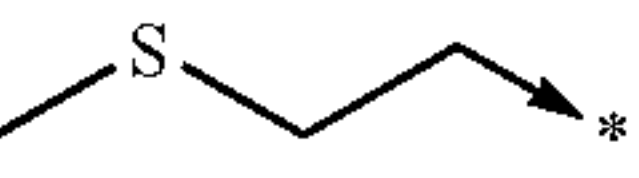
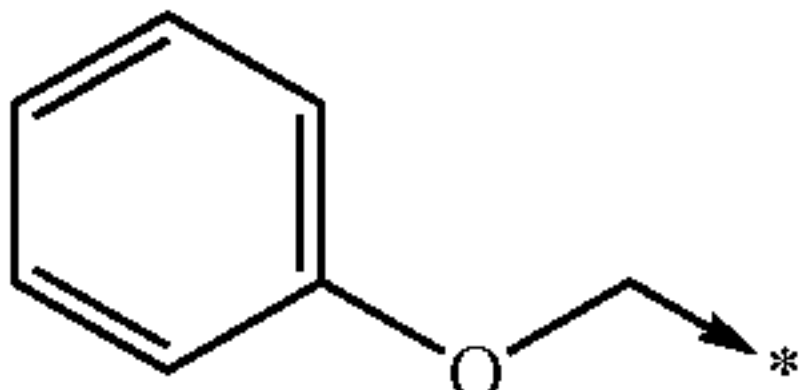
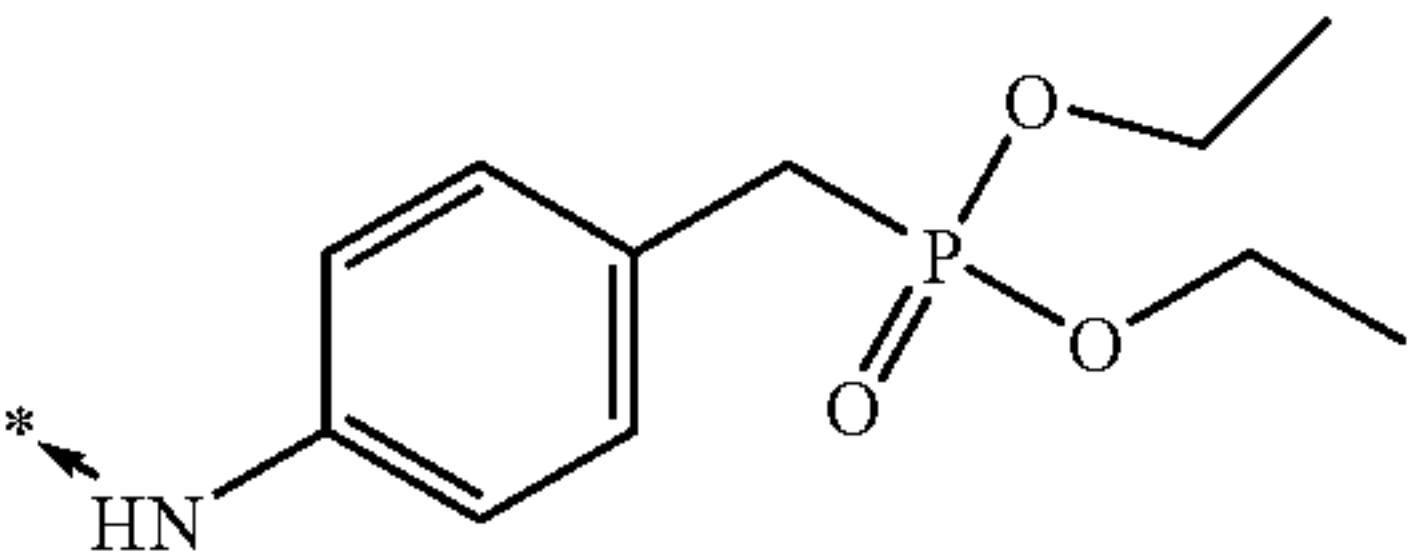
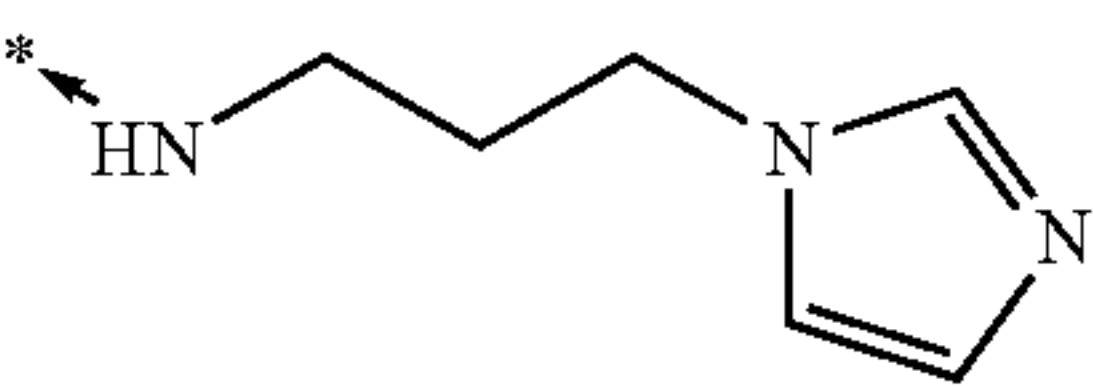
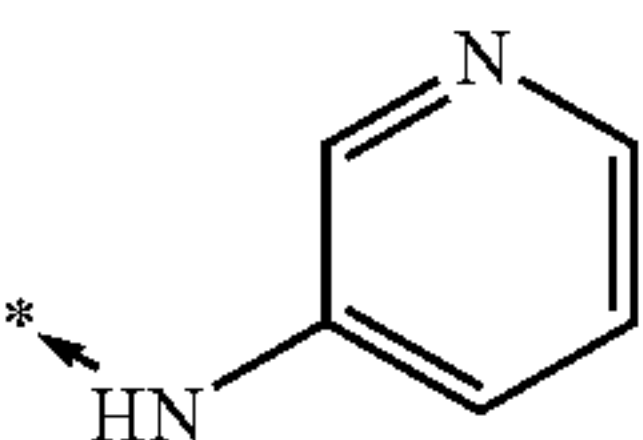
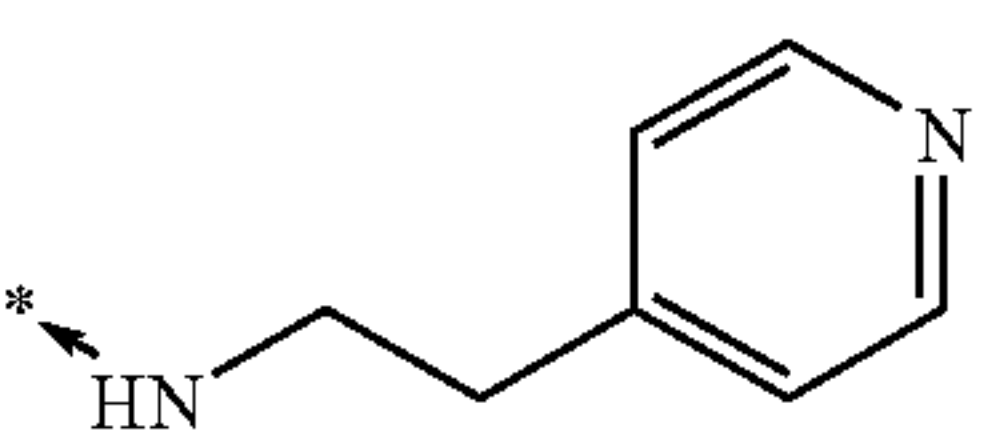
55

60

65

The structure and purity (HPLC retention time) and mass spectrum data of the object compounds are shown in [Table 6-1]–[Table 6-4], [Table 7-1]–[Table 7-4], [Table 8-1]–[Table 8-2], [Table 9-1]–[Table 9-4], [Table 10-1]–[Table 10-4], [Table 11-1]–[Table 11-4], [Table 12-1]–[Table 12-4], [Table 13-1]–[Table 13-4] and [Table 14].

TABLE 6-1

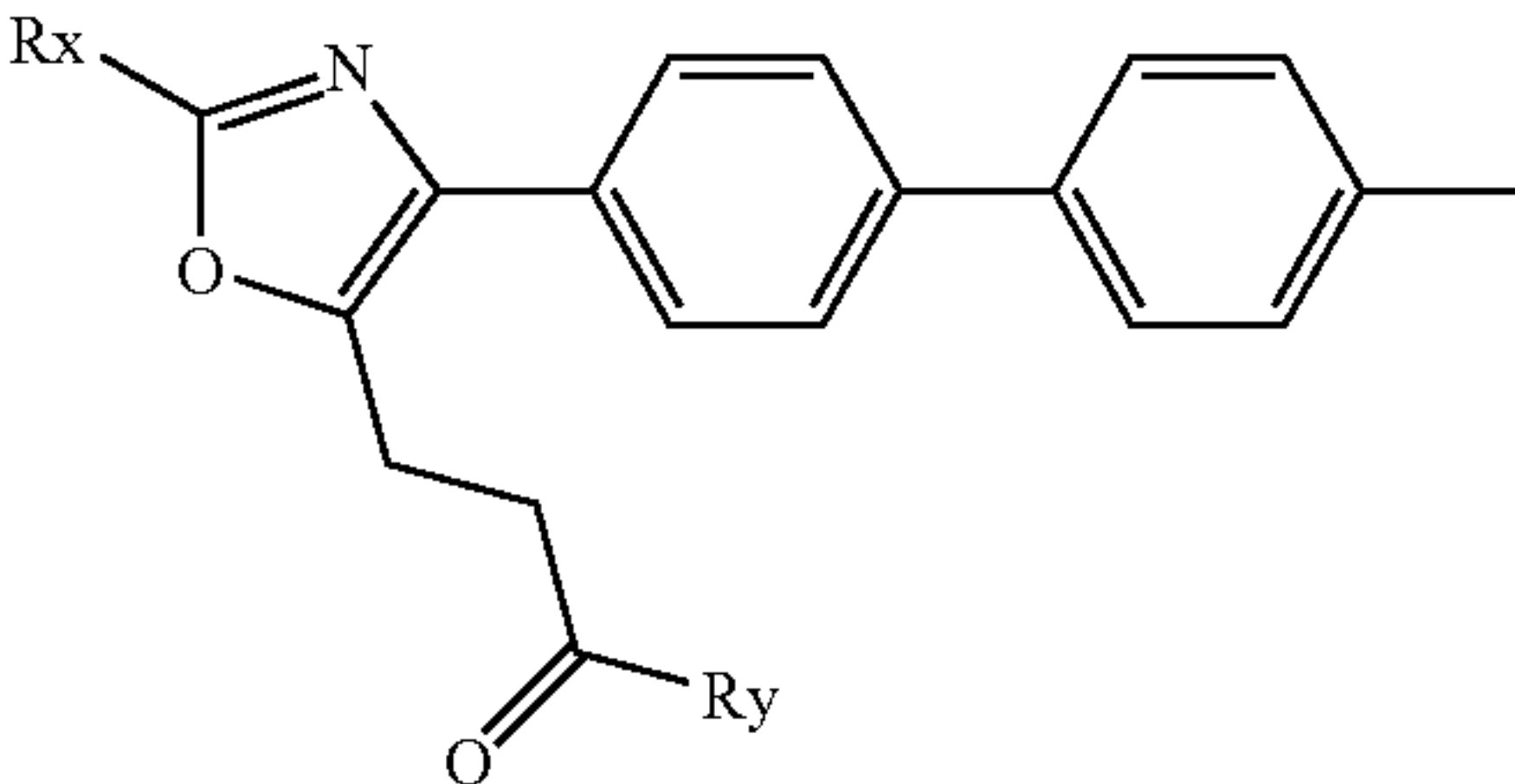
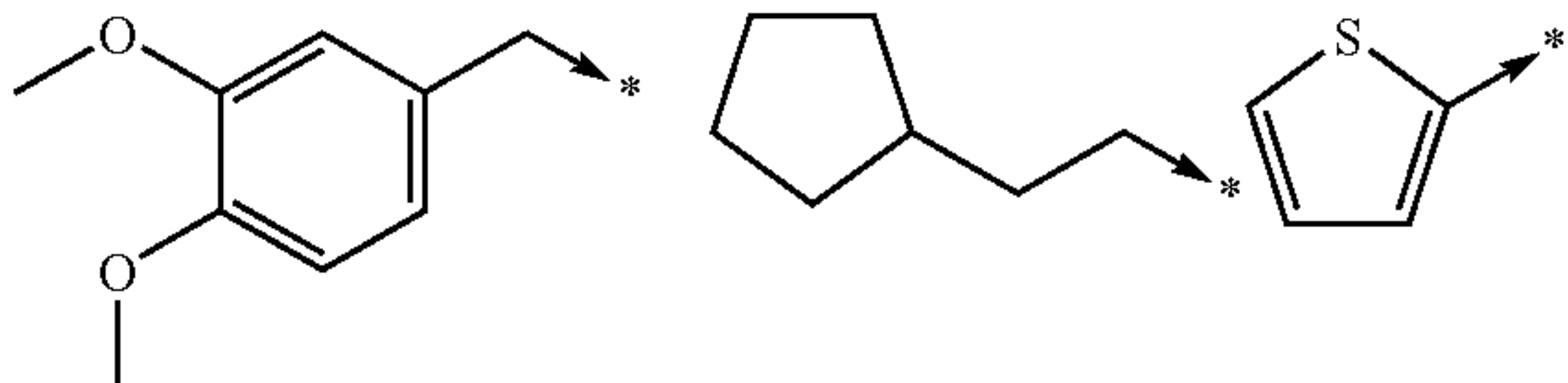
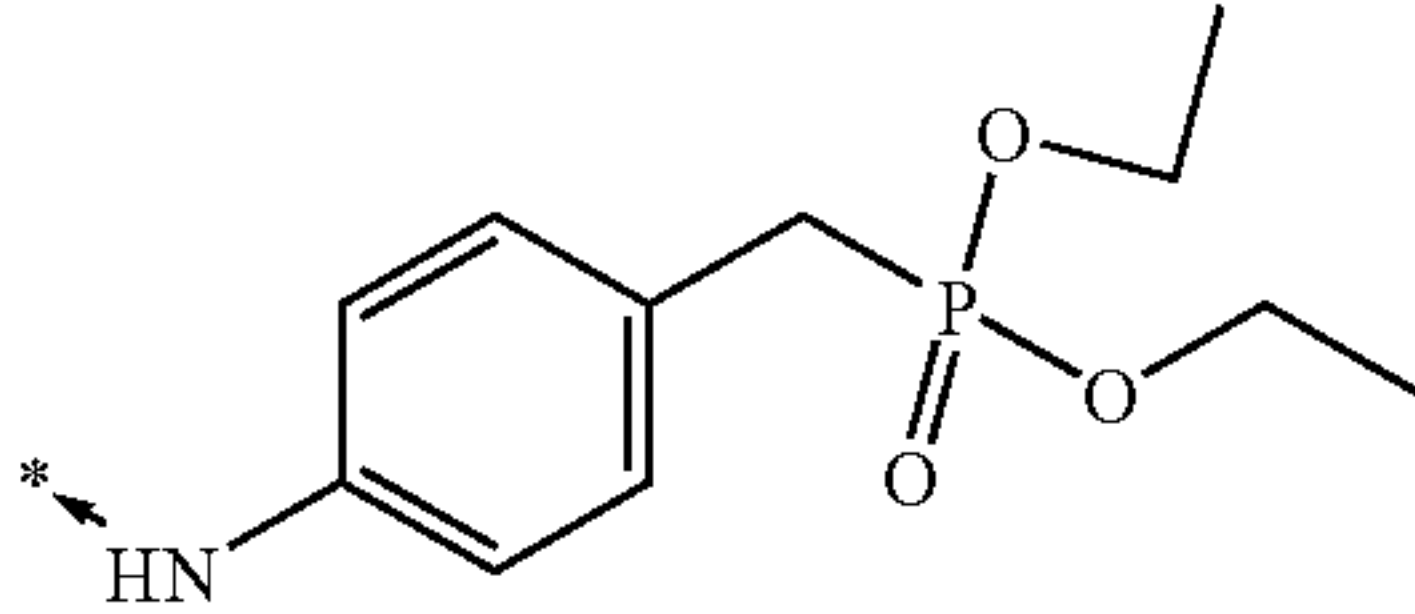
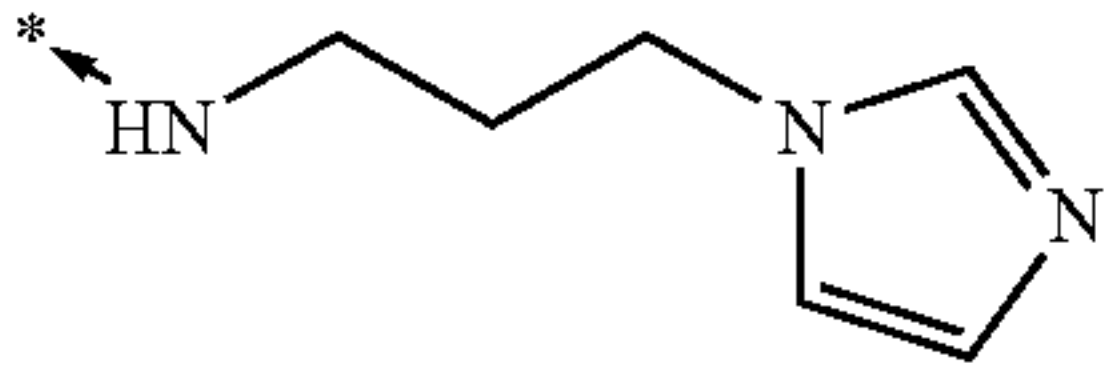
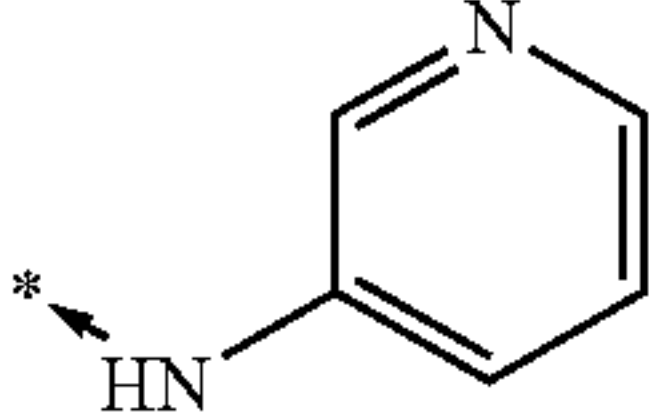
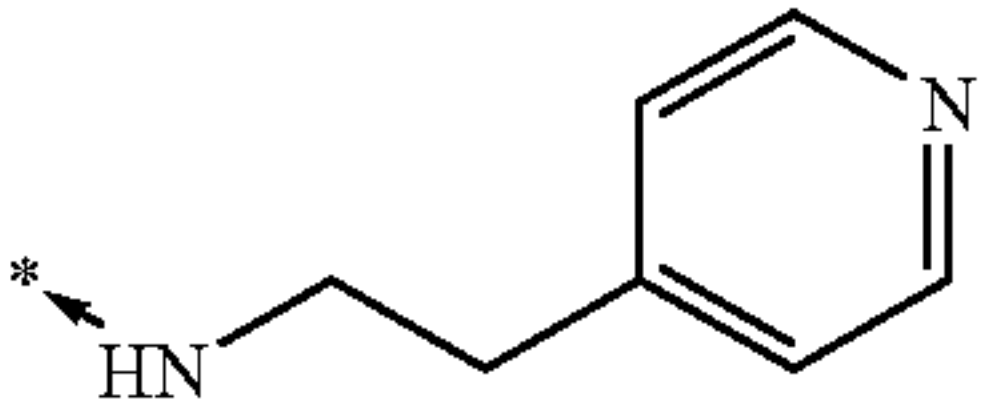
basic structure				
				
Rx				
Ry				
	Example 509 92%, 3.91 min 547(M + 1)	Example 510 99%, 4.64 min 631(M + 1)	Example 511 98%, 4.13 min 607(M + 1)	Example 512 100%, 4.32 min 639(M + 1)
	Example 516 93%, 2.99 min 429(M + 1)	Example 517 100%, 3.68 min 513(M + 1)	Example 518 98%, 3.21 min 489(M + 1)	Example 519 97%, 3.45 min 521(M + 1)
	Example 523 100%, 3.08 min 398(M + 1)	Example 524 99%, 3.78 min 482(M + 1)	Example 525 95%, 3.31 min 458(M + 1)	Example 526 98%, 3.53 min 490(M + 1)
	Example 530 94%, 2.98 min 426(M + 1)	Example 531 99%, 3.67 min 510(M + 1)	Example 532 96%, 3.20 min 486(M + 1)	Example 533 99%, 3.44 min 518(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time

lower line: MS(APCI+, m/e)

TABLE 6-2

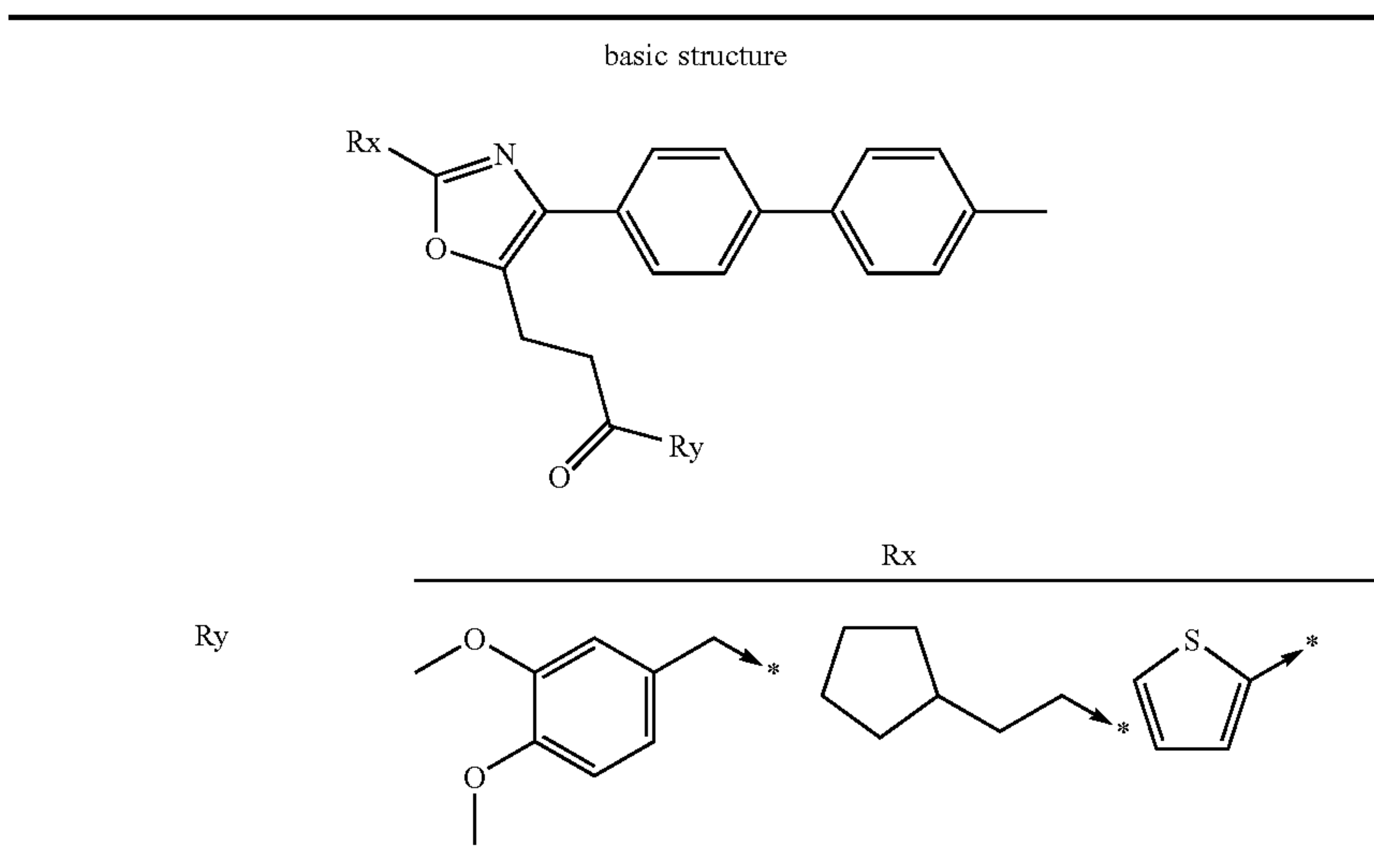
basic structure			
			
Rx			
Ry			
<hr/>			
	<p>Example 513 100%, 4.14 min 683(M + 1)</p>	<p>Example 514 99%, 4.62 min 629(M + 1)</p>	<p>Example 515 95%, 4.38 min 615(M + 1)</p>
	<p>Example 520 100%, 3.30 min 565(M + 1)</p>	<p>Example 521 87%, 3.65 min 511(M + 1)</p>	<p>Example 522 99%, 3.42 min 497(M + 1)</p>
	<p>Example 527 100%, 3.37 min 534(M + 1)</p>	<p>Example 528 98%, 3.74 min 480(M + 1)</p>	<p>Example 529 95%, 3.53 min 466(M + 1)</p>
	<p>Example 534 99%, 3.28 min 562(M + 1)</p>	<p>Example 535 97%, 3.64 min 508(M + 1)</p>	<p>Example 536 99%, 3.41 min 494(M + 1)</p>

upper line: Example No.

middle line: HPLC purity(220 nm), retention time

lower line: MS(APCI+, m/e)

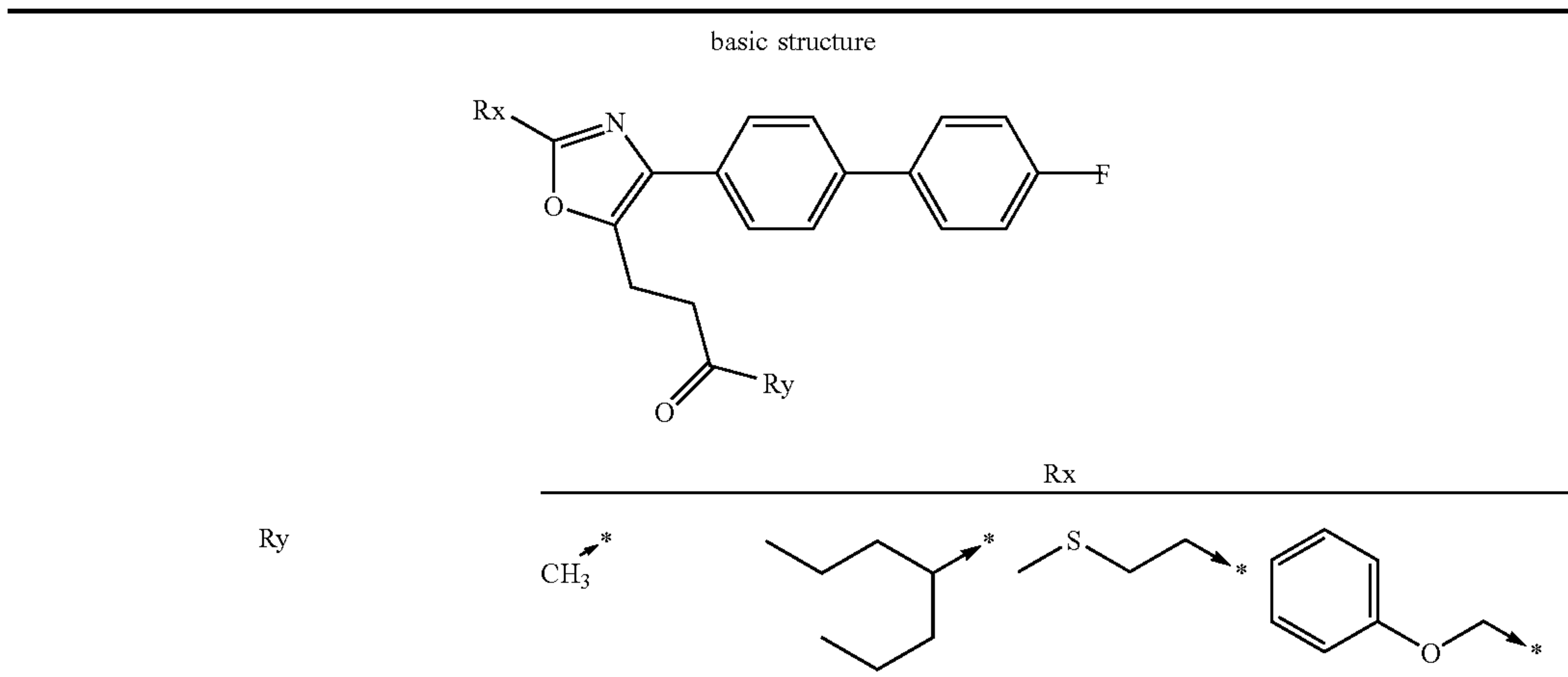
TABLE 6-4



	Example 541 100%, 3.81 min 563(M + 1)	Example 542 98%, 4.35 min 509(M + 1)	Example 543 100%, 4.04 min 495(M + 1)
	Example 548 100%, 3.31 min 570(M + 1)	Example 549 100%, 3.68 min 516(M + 1)	
	Example 554 98%, 3.31 min 540(M + 1)	Example 555 84%, 3.68 min 486(M + 1)	Example 556 94%, 3.45 min 472(M + 1)

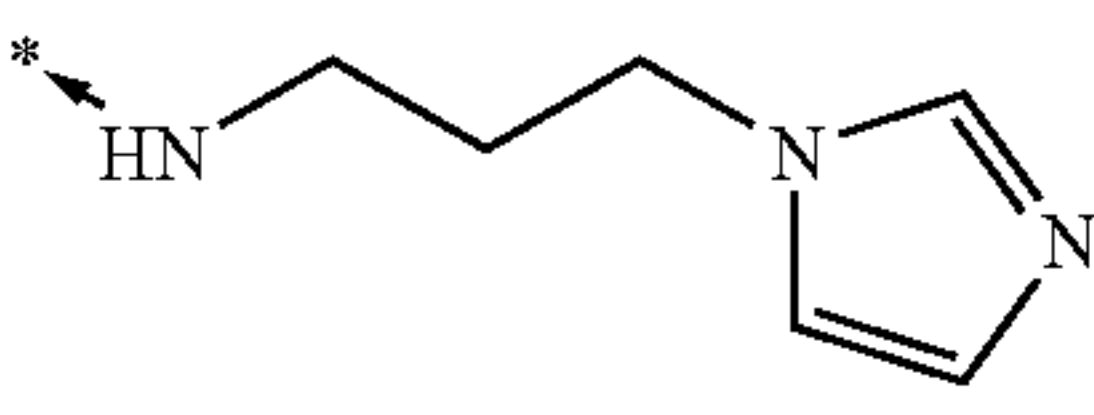
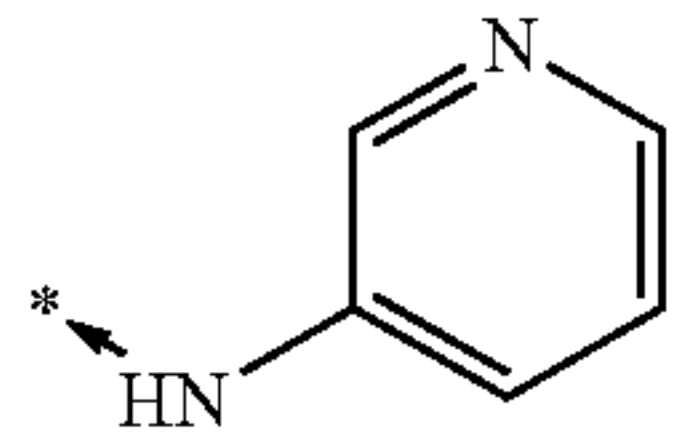
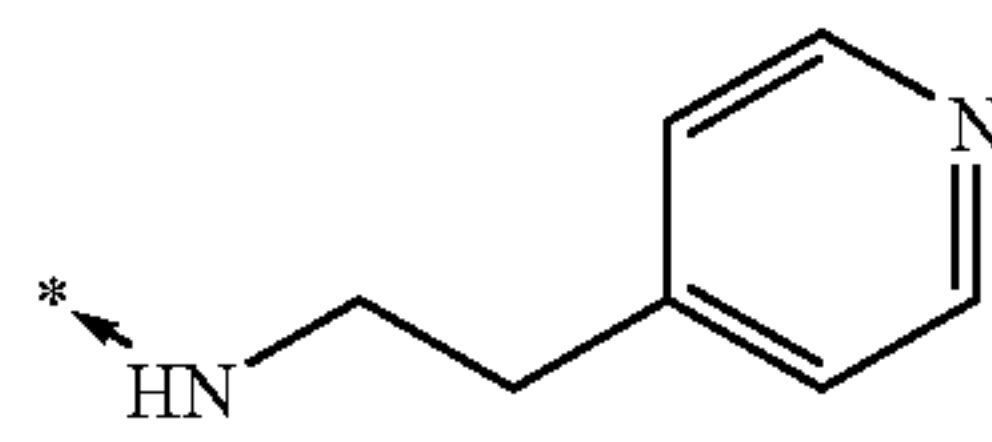
upper line: Example No.
middle line: HPLC purity(220 nm), retention time
lower line: MS(APCI+, m/e)

TABLE 7-1



	Example 557 96%, 3.81 min 551(M + 1)	Example 558 99%, 4.53 min 635(M + 1)	Example 559 100%, 4.02 min 611(M + 1)	Example 560 100%, 4.21 min 643(M + 1)
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TABLE 7-1-continued

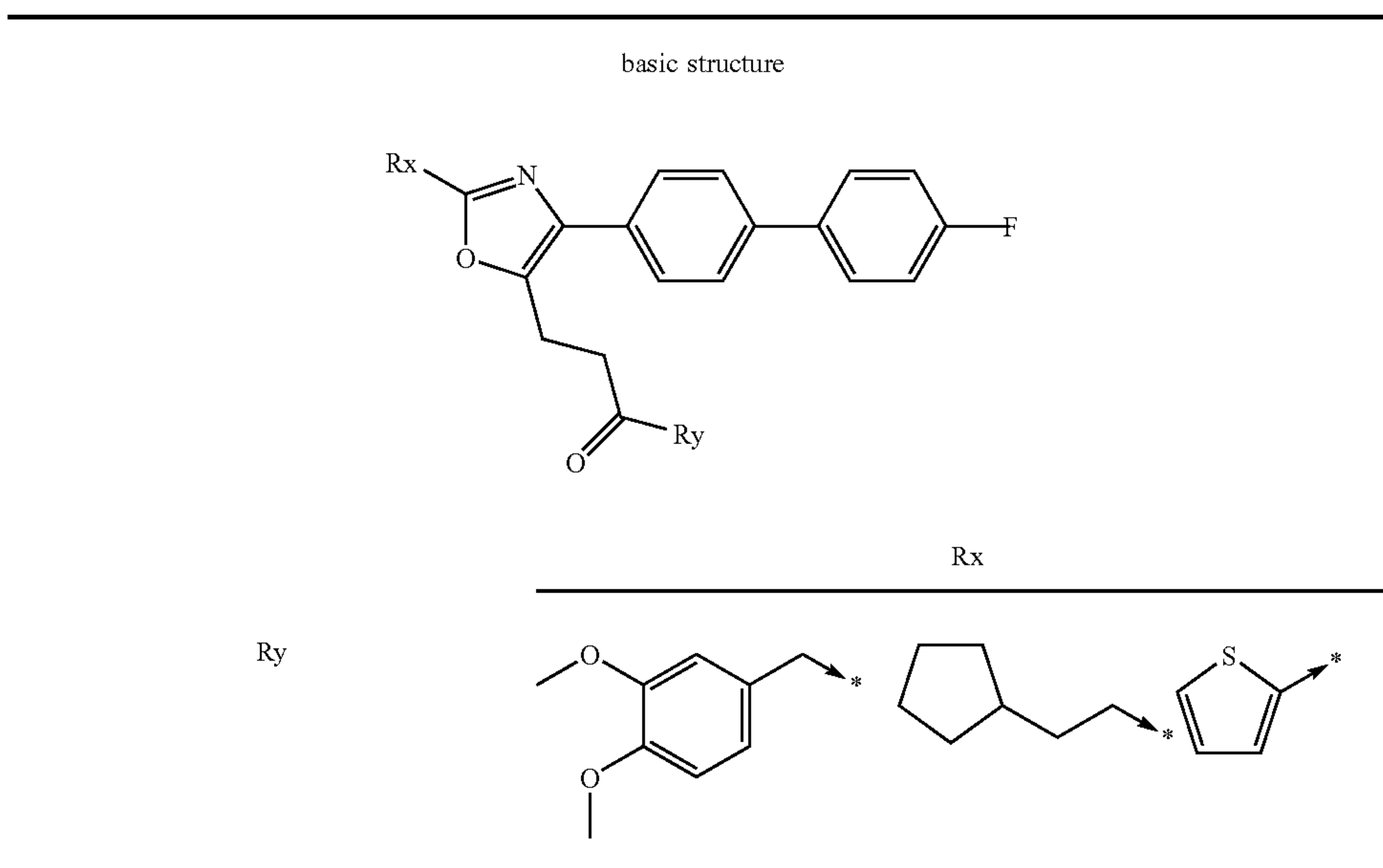
	Example 564 98%, 2.88 min 433(M + 1)	Example 565 90%, 3.59 min 517(M + 1)	Example 566 99%, 3.12 min 493(M + 1)	Example 567 93%, 3.36 min 525(M + 1)
	Example 571 96%, 2.97 min 402(M + 1)	Example 572 100%, 3.69 min 486(M + 1)	Example 573 94%, 3.20 min 462(M + 1)	Example 574 98%, 3.44 min 494(M + 1)
	Example 578 93%, 2.88 min 430(M + 1)	Example 579 91%, 3.58 min 514(M + 1)	Example 580 96%, 3.11 min 490(M + 1)	Example 581 89%, 3.34 min 522(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time

lower line: MS(APCI+, m/e)

TABLE 7-2



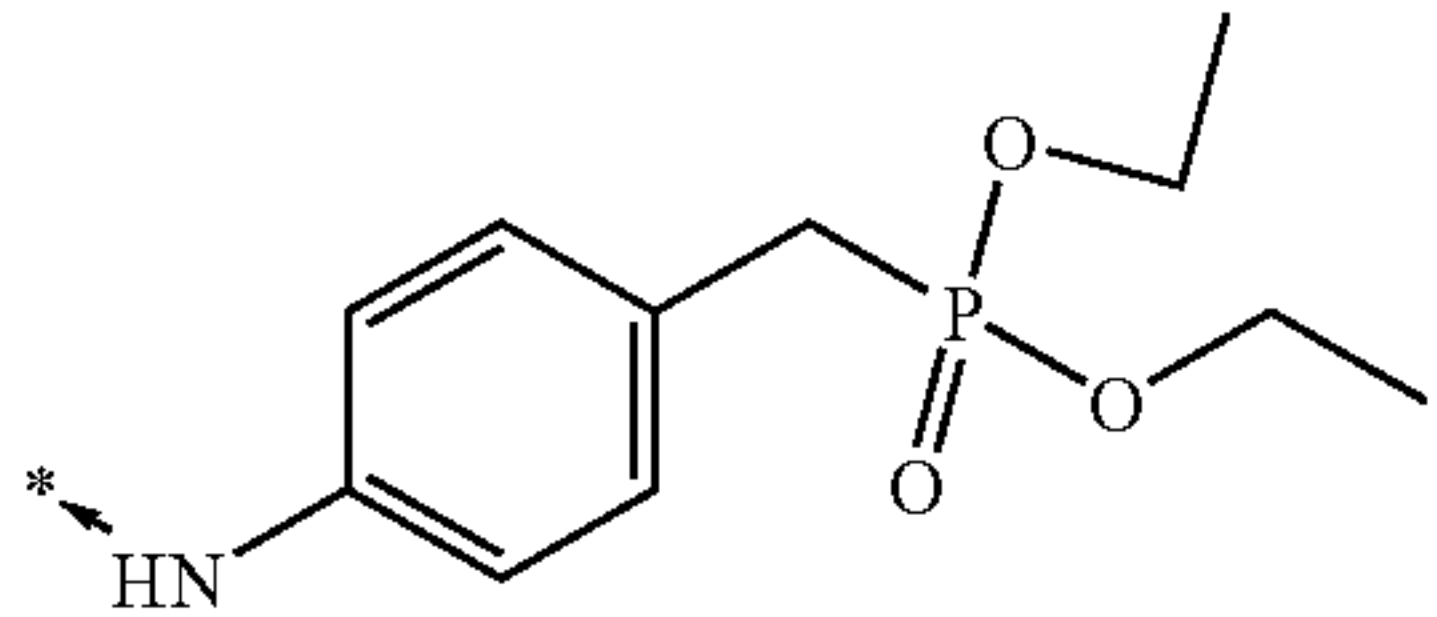
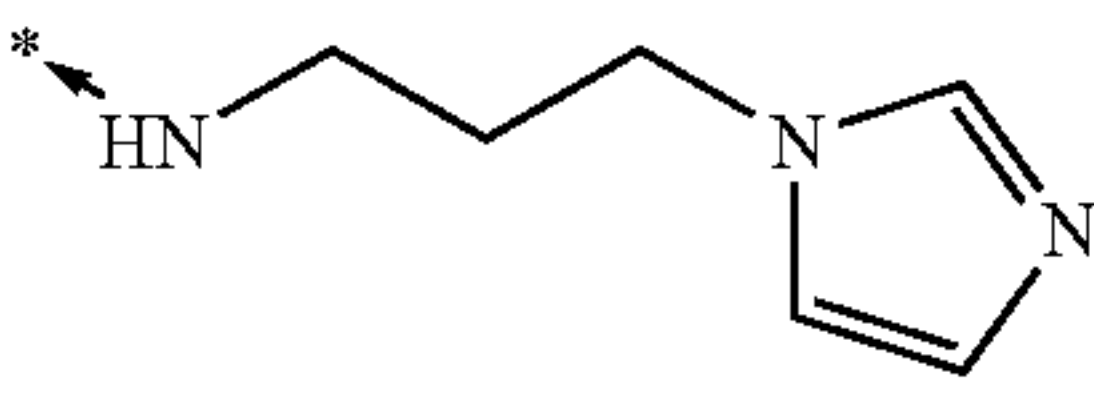
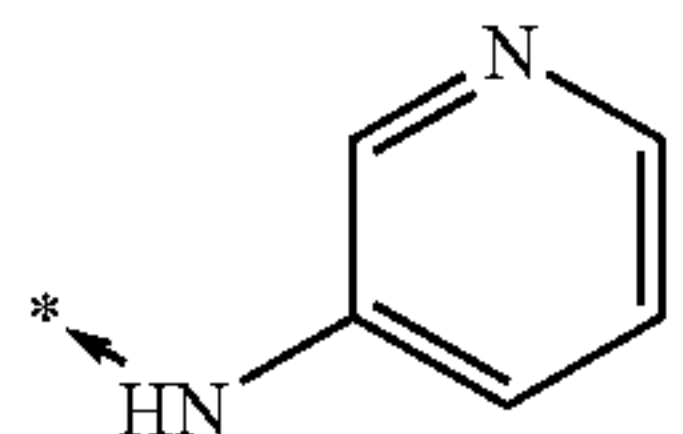
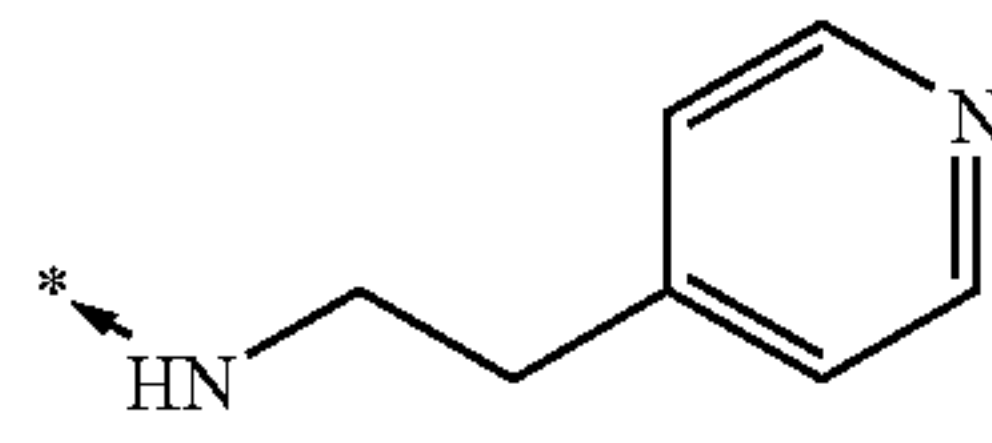
	Example 561 100%, 4.04 min 687(M + 1)	Example 562 96%, 4.51 min 633(M + 1)	Example 563 100%, 4.27 min 619(M + 1)
	Example 568 95%, 3.21 min 569(M + 1)	Example 569 88%, 3.57 min 515(M + 1)	Example 570 100%, 3.33 min 501(M + 1)
	Example 575 98%, 3.28 min 538(M + 1)	Example 576 97%, 3.67 min 484(M + 1)	Example 577 98%, 3.44 min 470(M + 1)

TABLE 7-2-continued

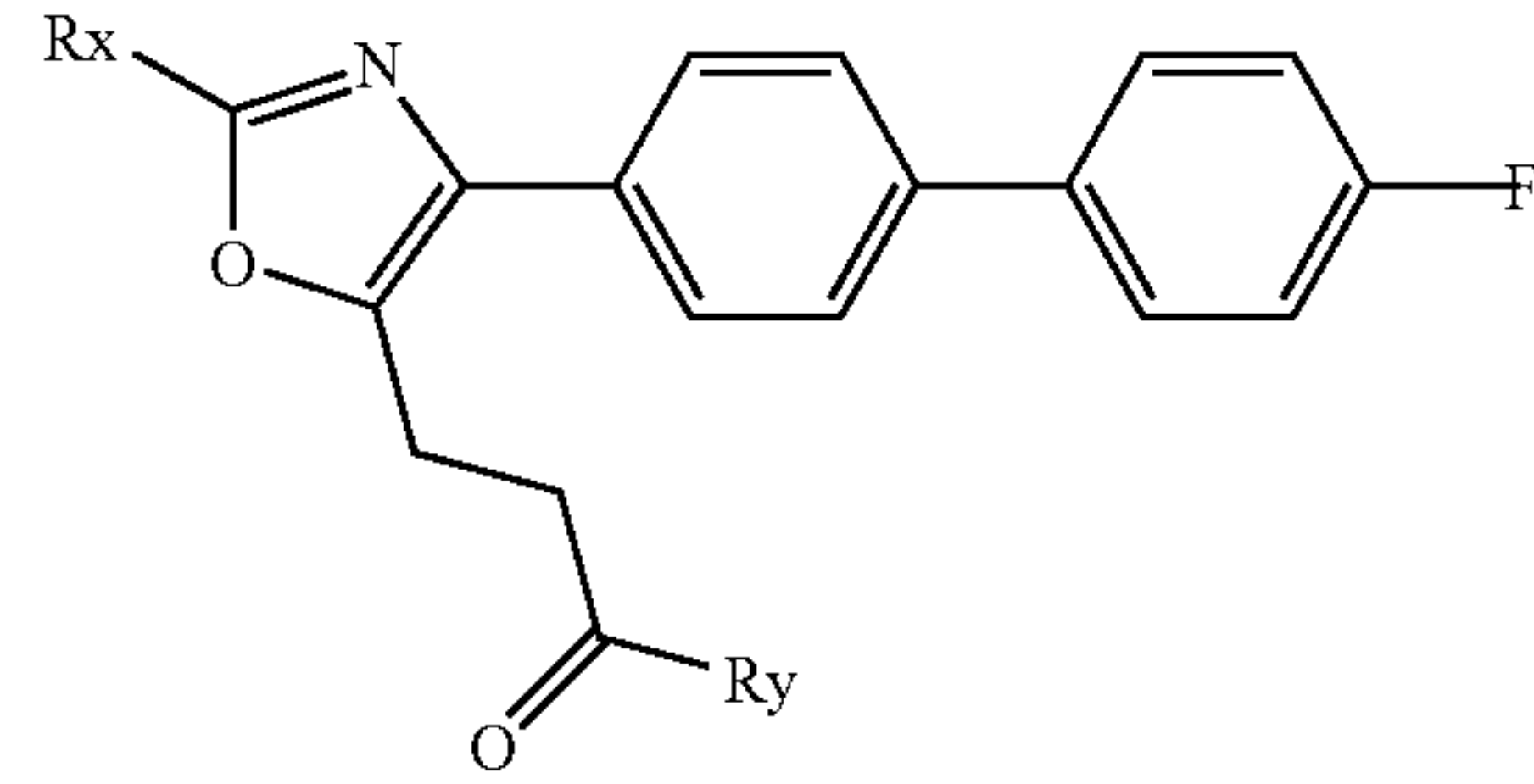
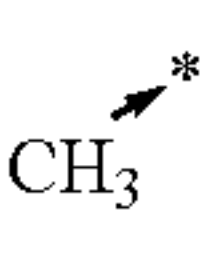
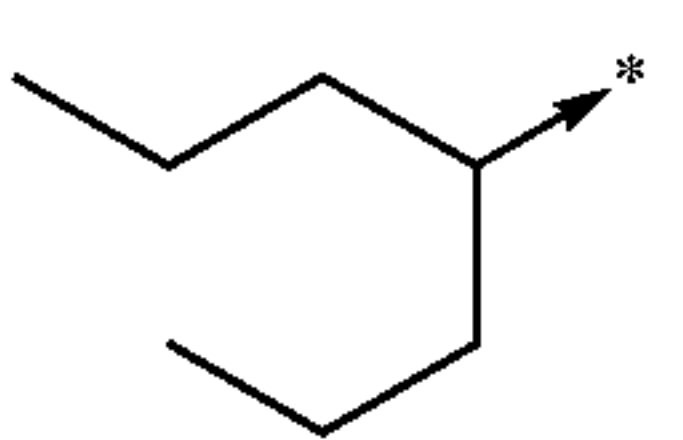
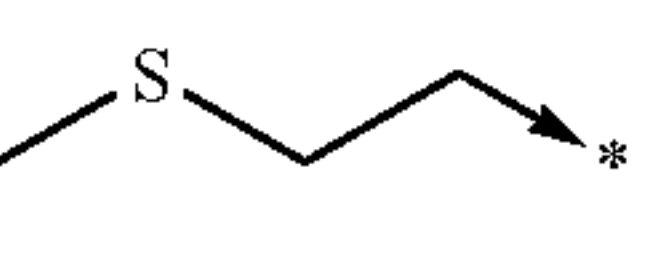
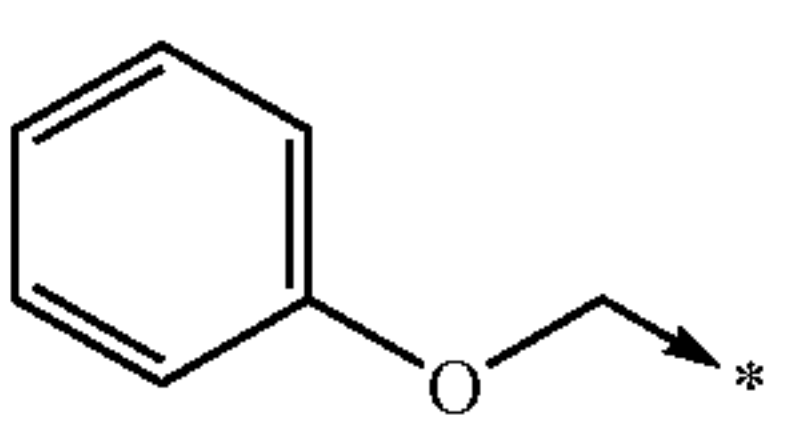
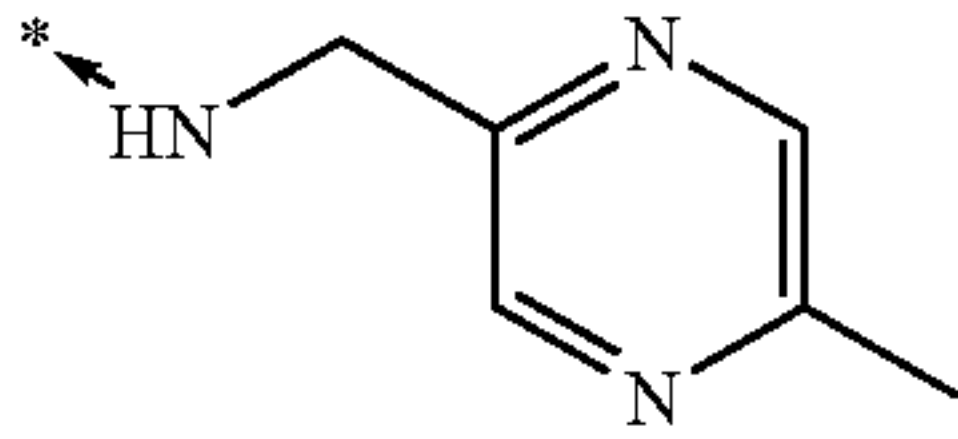
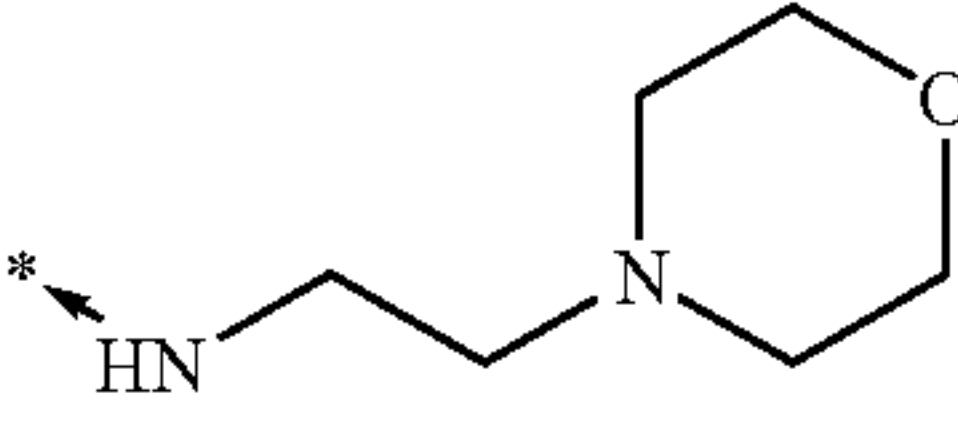
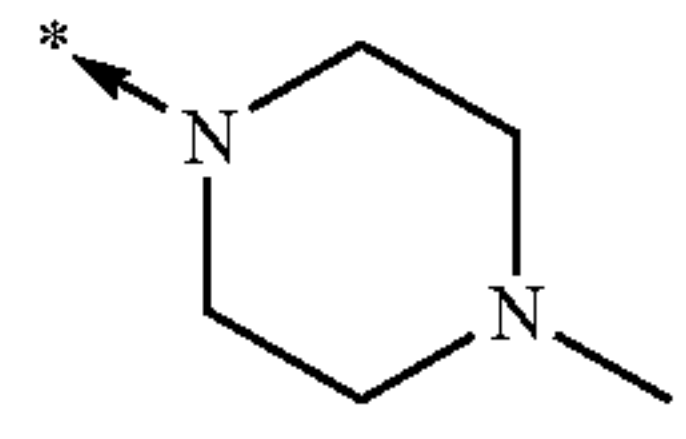
	Example 582 92%, 3.20 min 566(M + 1)	Example 583 89%, 3.56 min 512(M + 1)	Example 584 98%, 3.33 min 498(M + 1)
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upper line: Example No.

middle line: HPLC purity(220 nm), retention time

lower line: MS(APCI+, m/e)

TABLE 7-3

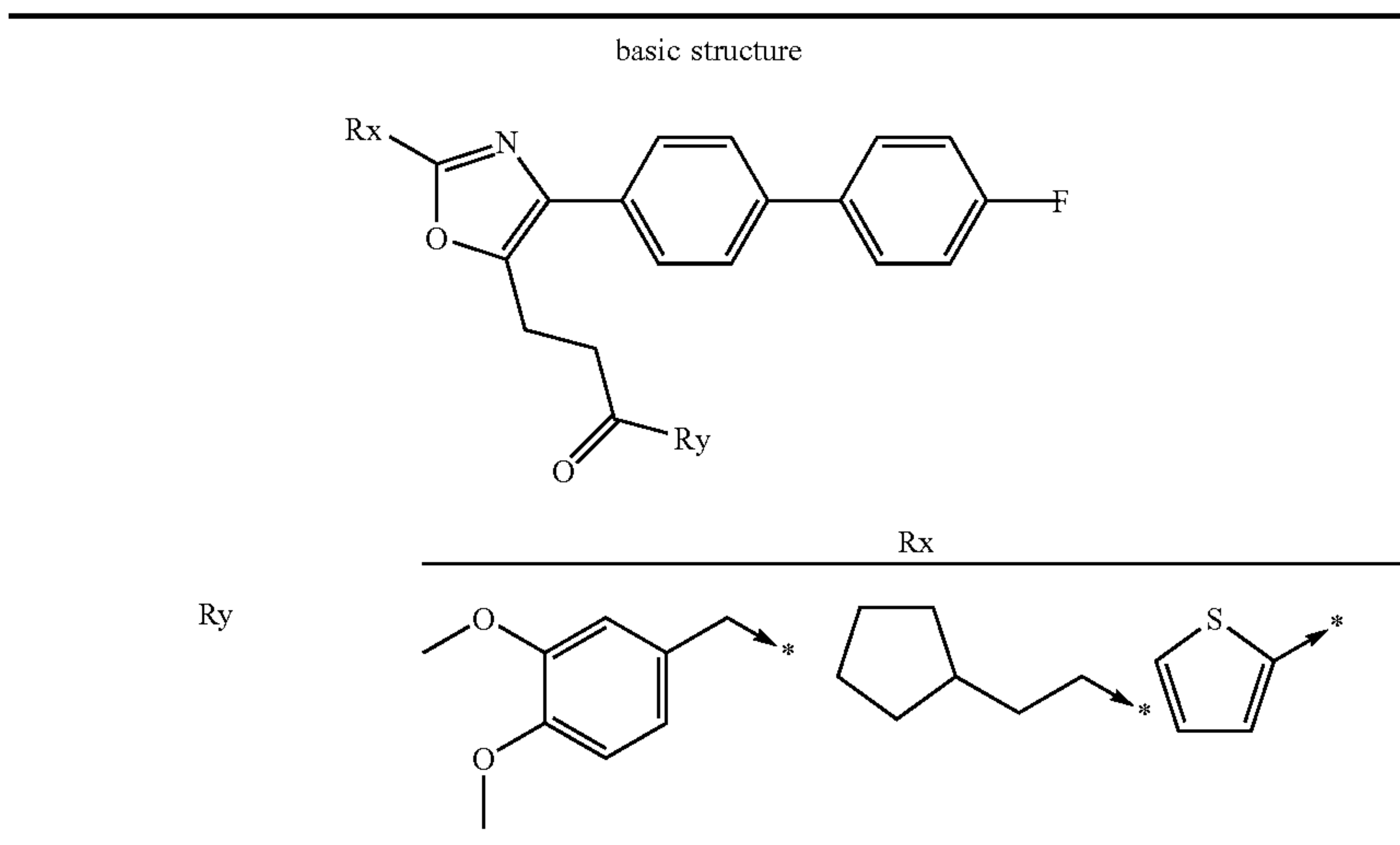
basic structure				
				
Rx				
Ry				
	Example 585 100%, 3.38 min 431(M + 1)	Example 586 97%, 4.28 min 515(M + 1)	Example 587 100%, 3.66 min 491(M + 1)	Example 588 99%, 3.92 min 523(M + 1)
	Example 592 92%, 2.90 min 438(M + 1)	Example 593 94%, 3.62 min 522(M + 1)	Example 594 93%, 3.14 min 498(M + 1)	Example 595 99%, 3.38 min 530(M + 1)
	Example 599 89%, 2.90 min 408(M + 1)	Example 600 91%, 3.61 min 492(M + 1)	Example 601 92%, 3.14 min 468(M + 1)	Example 602 98%, 3.38 min 500(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time

lower line: MS(APCI+, m/e)

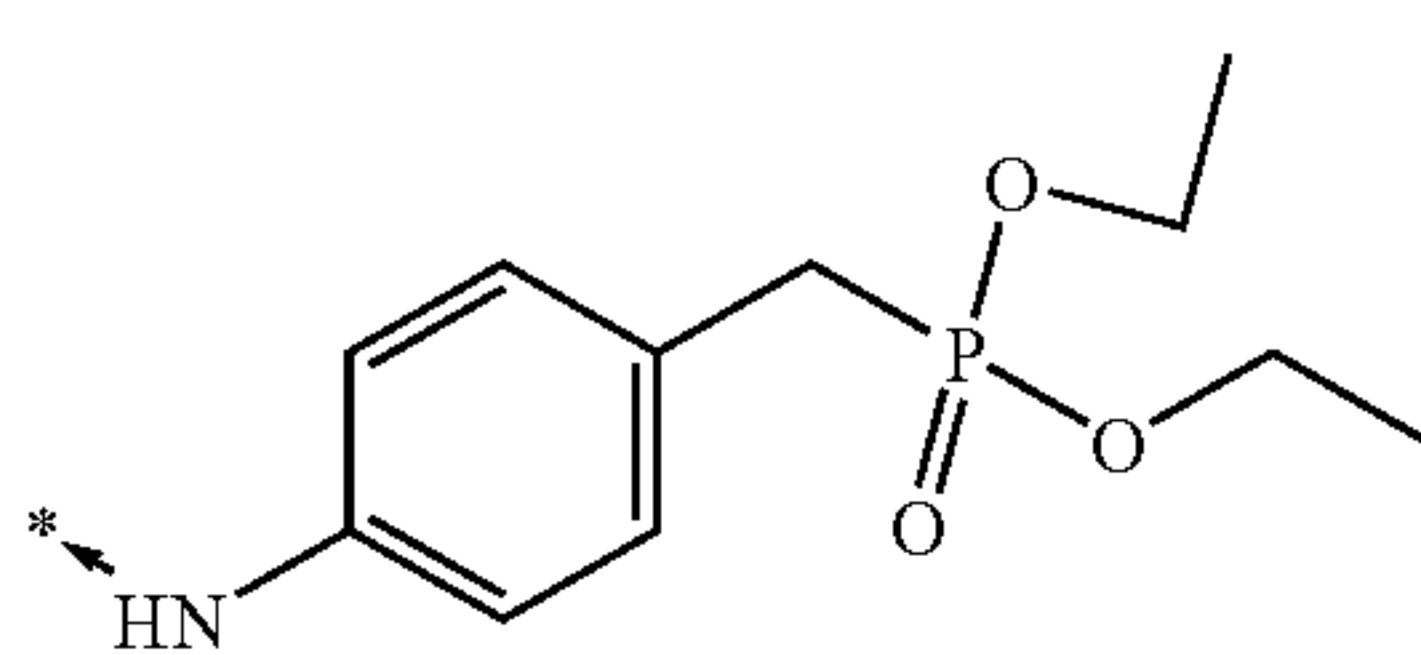
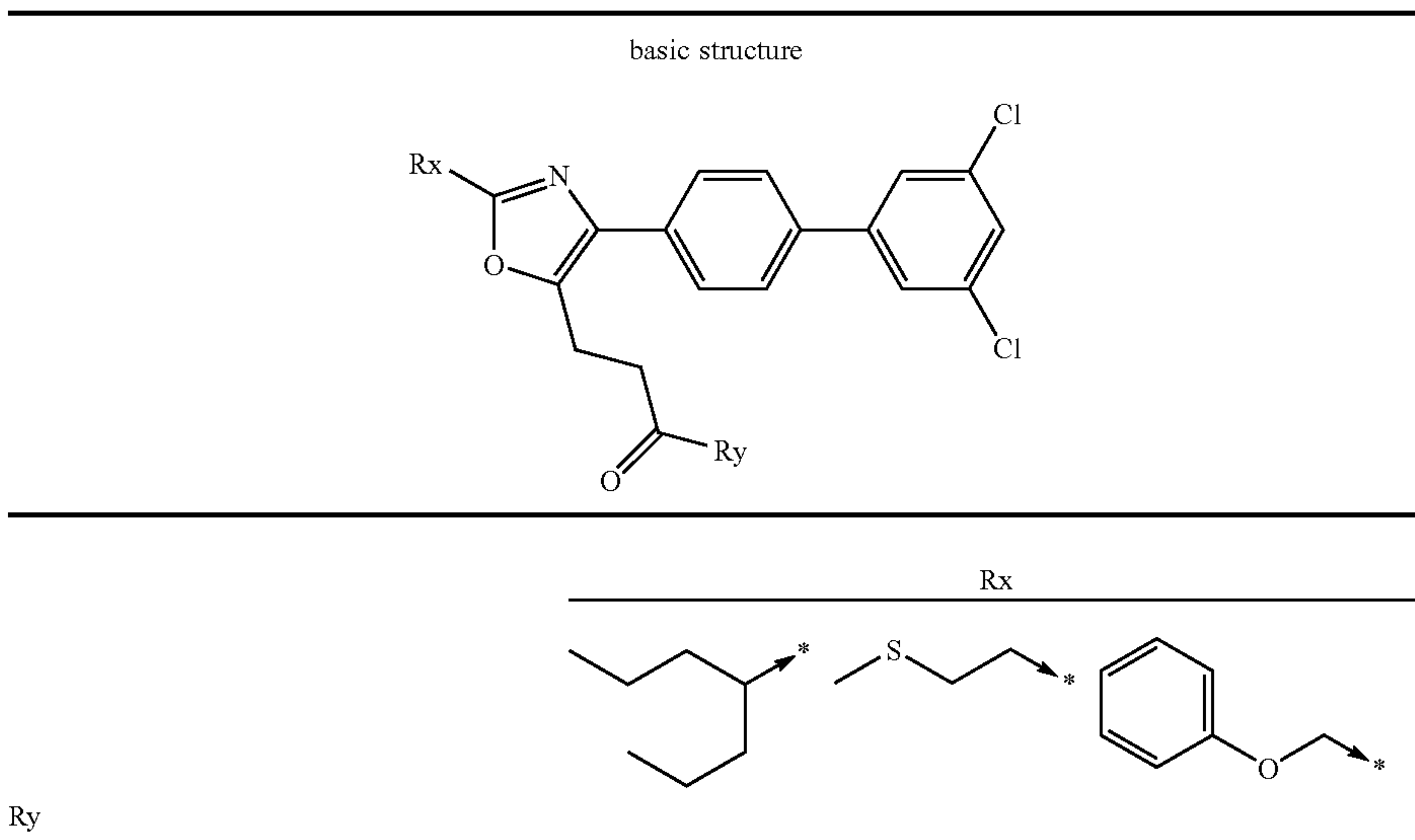
TABLE 7-4



	<p>Example 589 100%, 3.71 min 567(M + 1)</p>	<p>Example 590 97%, 4.24 min 513(M + 1)</p>	<p>Example 591 100%, 3.92 min 499(M + 1)</p>
	<p>Example 596 95%, 3.22 min 574(M + 1)</p>	<p>Example 597 90%, 3.59 min 520(M + 1)</p>	<p>Example 598 98%, 3.35 min 506(M + 1)</p>
	<p>Example 603 91%, 3.23 min 544(M + 1)</p>	<p>Example 604 91%, 3.58 min 490(M + 1)</p>	<p>Example 605 92%, 3.35 min 476(M + 1)</p>

upper line: Example No.
middle line: HPLC purity(220 nm), retention time
lower line: MS(APCI+, m/e)

TABLE 8-1



Example 606
100%, 4.61 min
693(M + 1)

TABLE 8-1-continued

basic structure			
	Example 609 98%, 3.95 min 567(M + 1)	Example 610 99%, 3.47 min 543(M + 1)	Example 611 100%, 3.68 min 575(M + 1)
		Example 614 94%, 3.58 min 512(M + 1)	Example 615 98%, 3.78 min 544(M + 1)
	Example 618 99%, 3.95 min 564(M + 1)	Example 619 96%, 3.47 min 540(M + 1)	Example 620 99%, 3.68 min 572(M + 1)
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>Ry</p> </div> <div style="text-align: center;"> <p>Rx</p> </div> </div>			
	Example 607 100%, 4.44 min 737(M + 1)	Example 608 100%, 4.97 min 683(M + 1)	
	Example 612 99%, 3.54 min 619(M + 1)	Example 613 99%, 3.92 min 565(M + 1)	
	Example 616 98%, 3.63 min 588(M + 1)	Example 617 100%, 4.03 min 534(M + 1)	
	Example 621 100%, 3.53 min 616(M + 1)	Example 622 99%, 3.91 min 562(M + 1)	

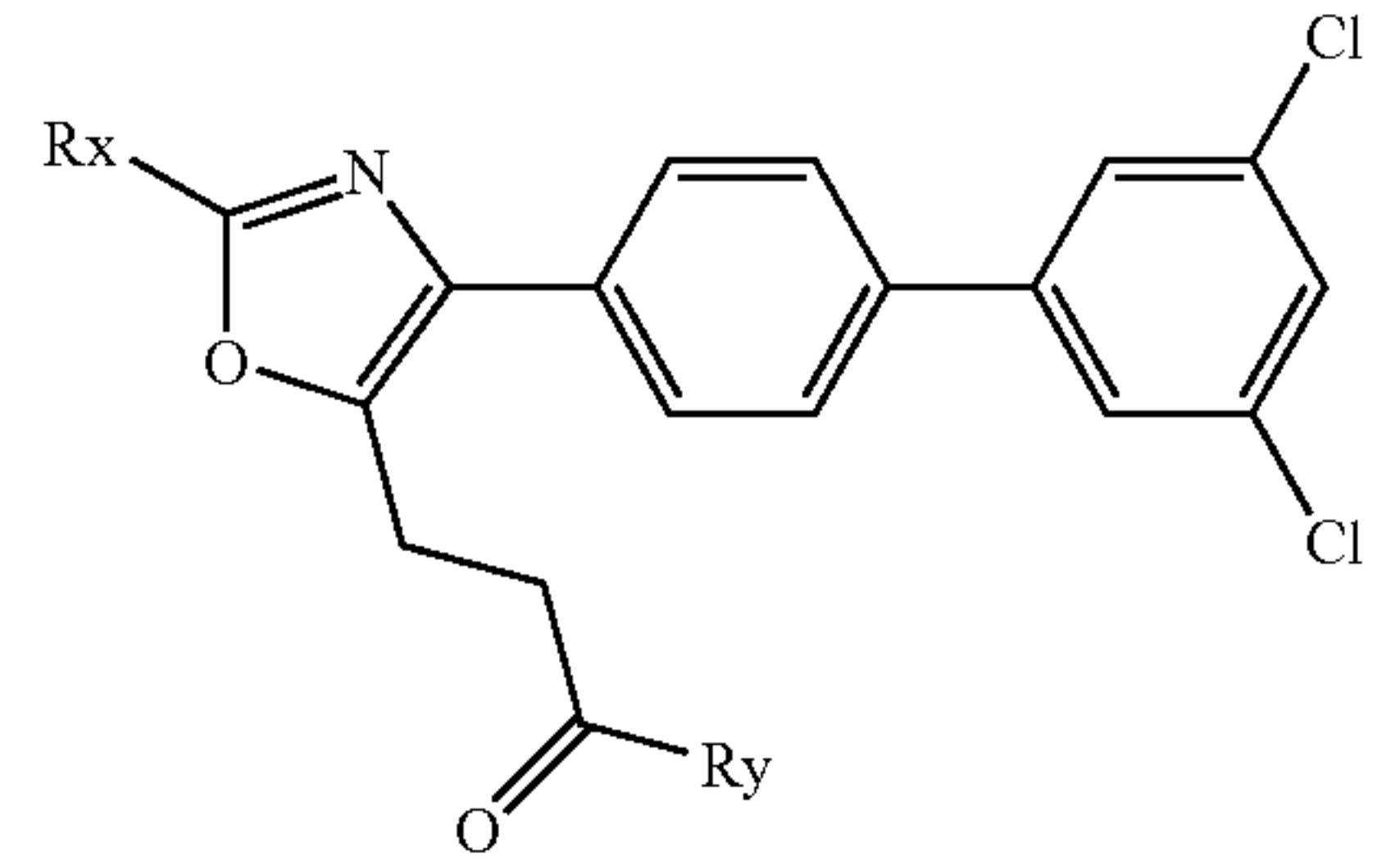
upper line: Example No.

middle line: HPLC purity(220 nm), retention time

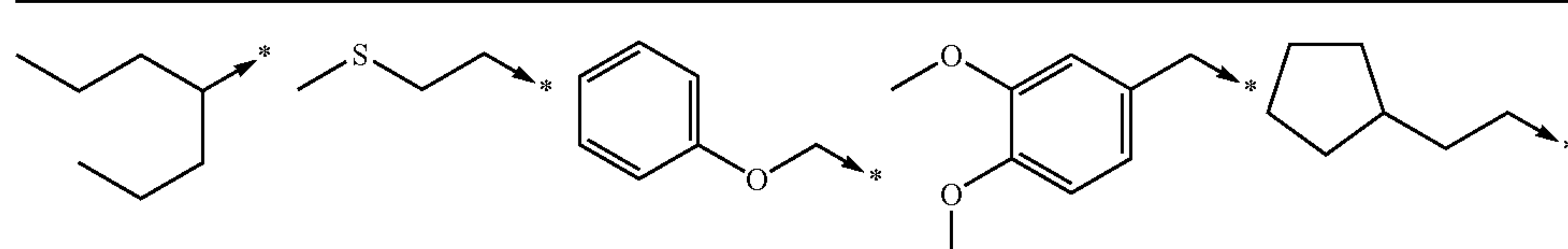
lower line: MS(APCI+, m/e)

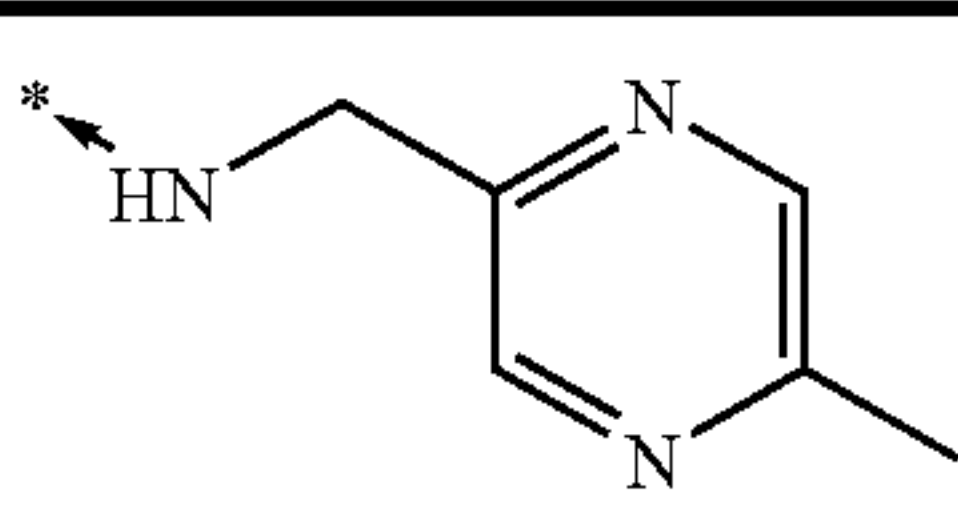
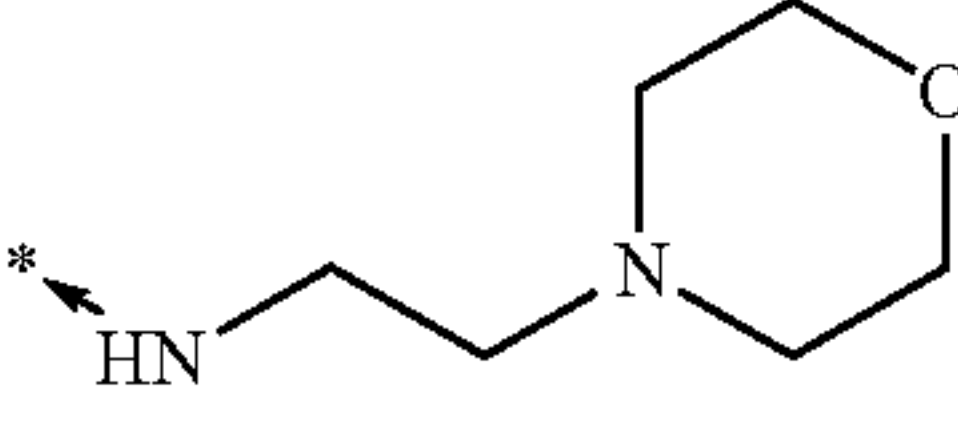
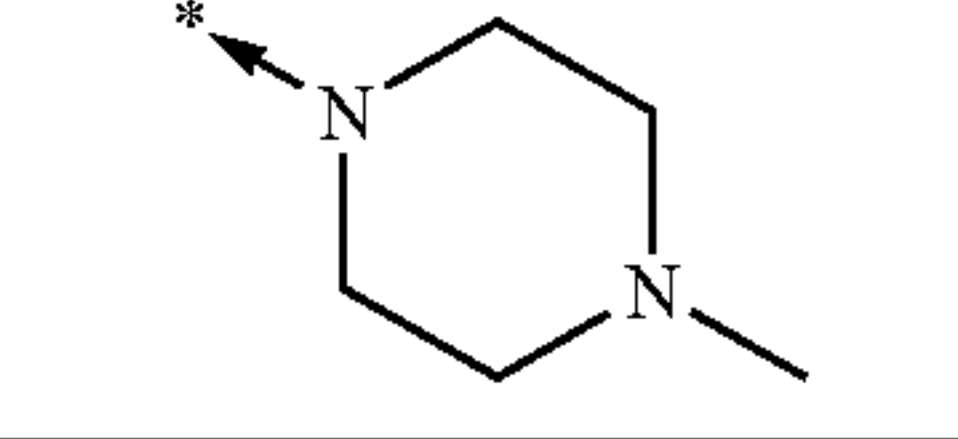
TABLE 8-2

basic structure



Ry

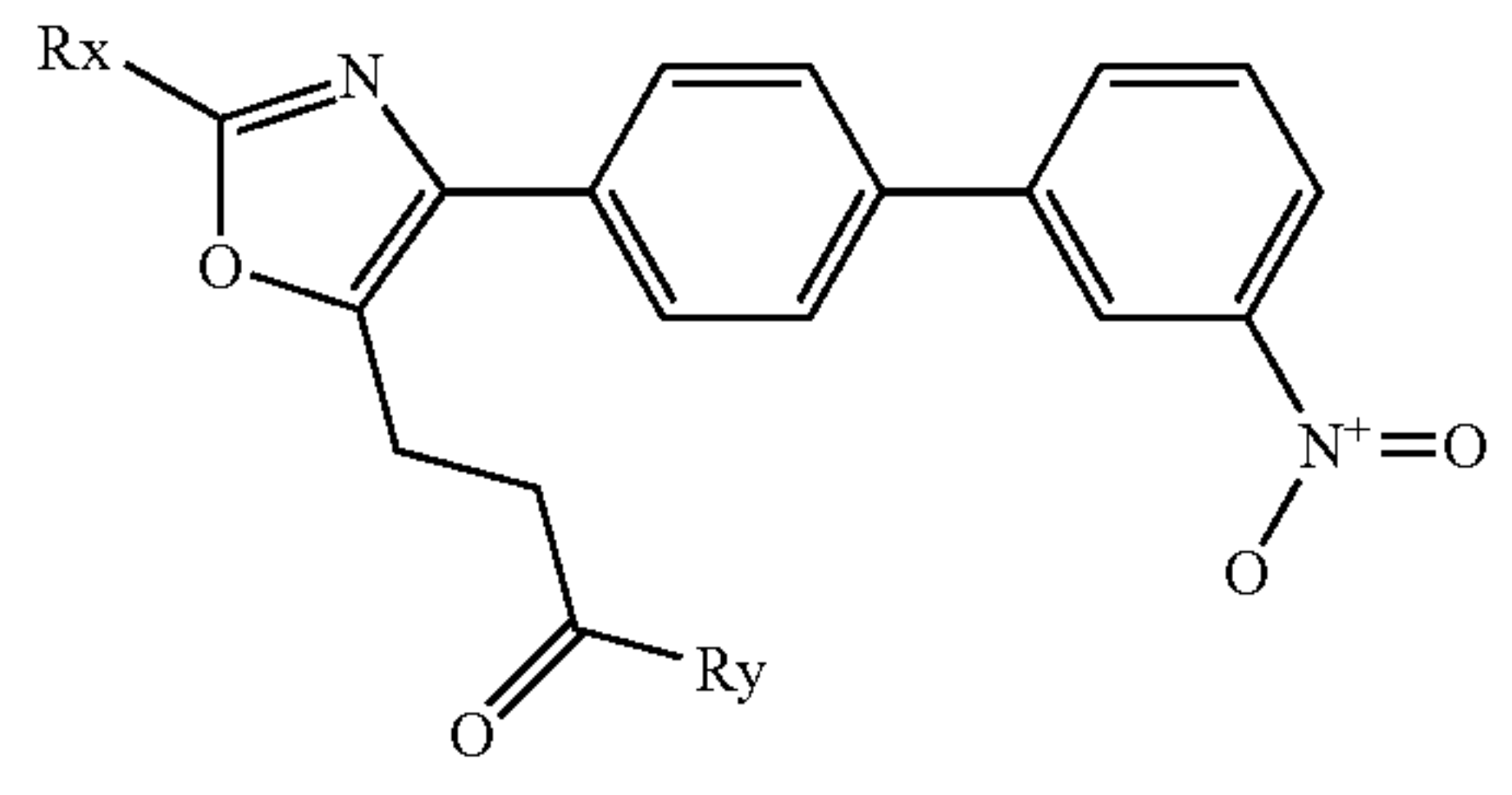


	Example 623 98%, 4.76 min 565(M + 1)	Example 624 94%, 4.12 min 541(M + 1)	Example 625 100%, 4.34 min 573(M + 1)	Example 626 100%, 4.14 min 617(M + 1)	Example 627 98%, 4.71 min 563(M + 1)
	Example 628 100%, 3.97 min 572(M + 1)	Example 629 99%, 3.48 min 548(M + 1)	Example 630 99%, 3.70 min 580(M + 1)	Example 631 100%, 3.55 min 624(M + 1)	Example 632 95%, 3.94 min 570(M + 1)
	Example 633 99%, 3.97 min 542(M + 1)	Example 634 96%, 3.49 min 518(M + 1)	Example 635 98%, 3.70 min 550(M + 1)	Example 636 98%, 3.55 min 594(M + 1)	Example 637 97%, 3.93 min 540(M + 1)

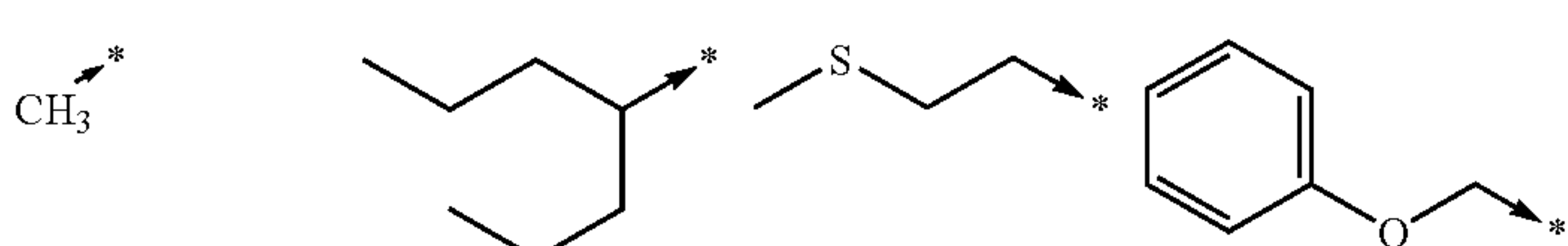
upper line: Example No.
middle line: HPLC purity(220 nm), retention time
lower line: MS(APCI+, m/e)

TABLE 9-1

basic structure



Ry



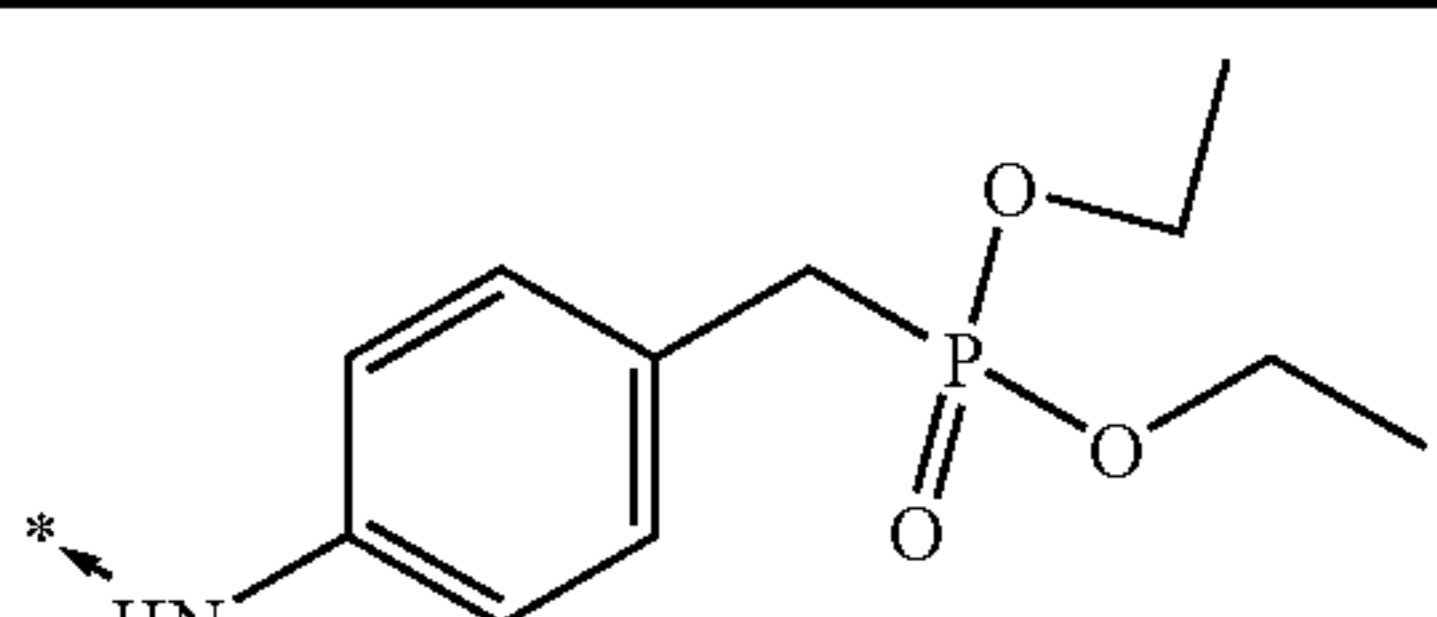
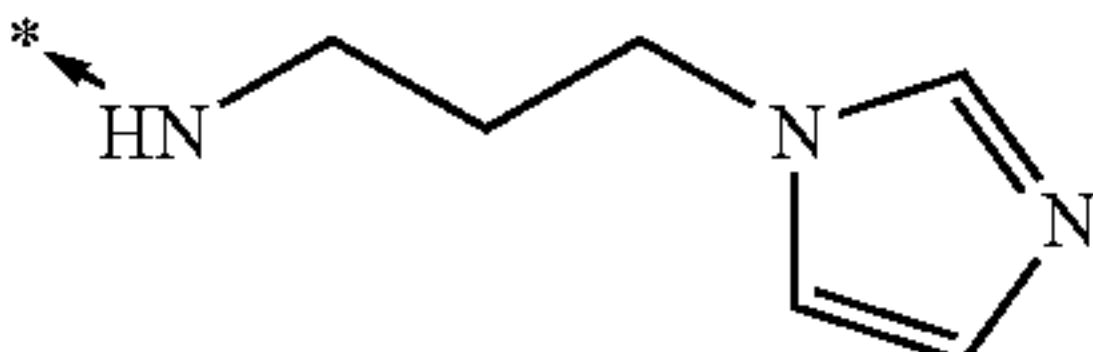
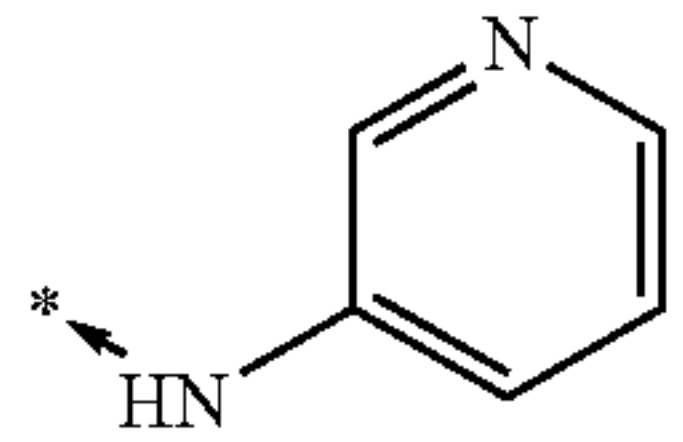
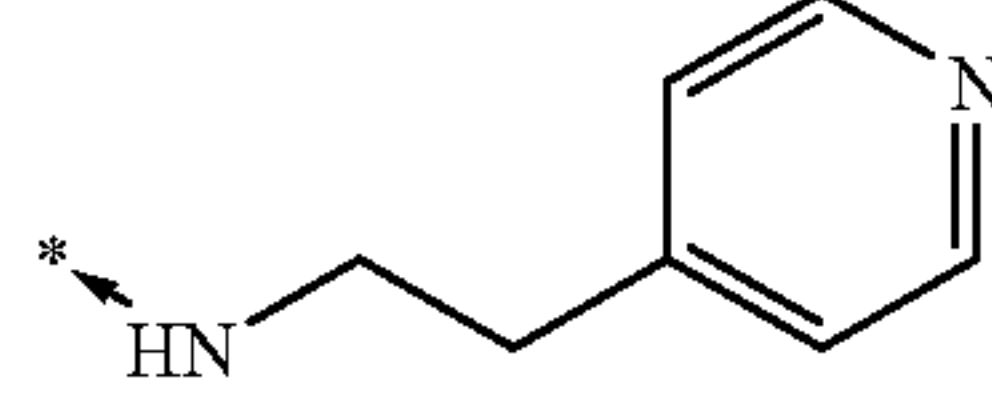
	Example 638 100%, 3.77 min 578(M + 1)	Example 639 98%, 4.49 min 662(M + 1)	Example 640 88%, 3.98 min 638(M + 1)	Example 641 100%, 4.16 min 670(M + 1)
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TABLE 9-1-continued

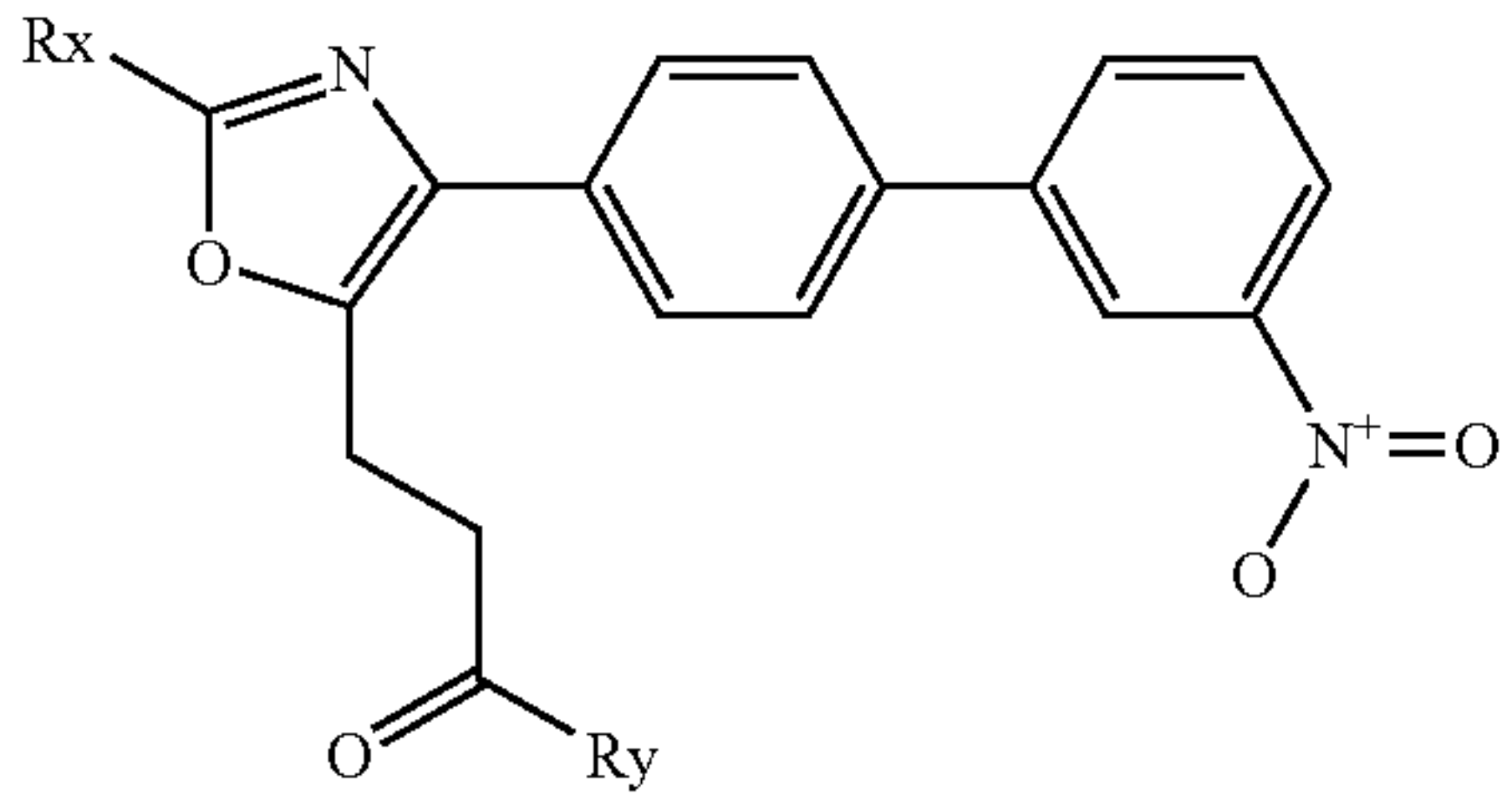
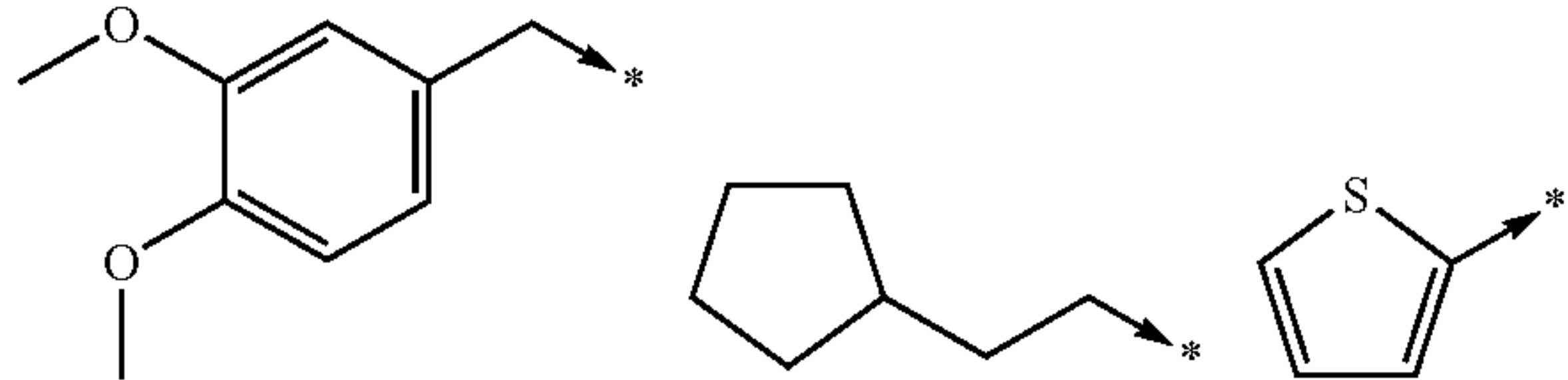
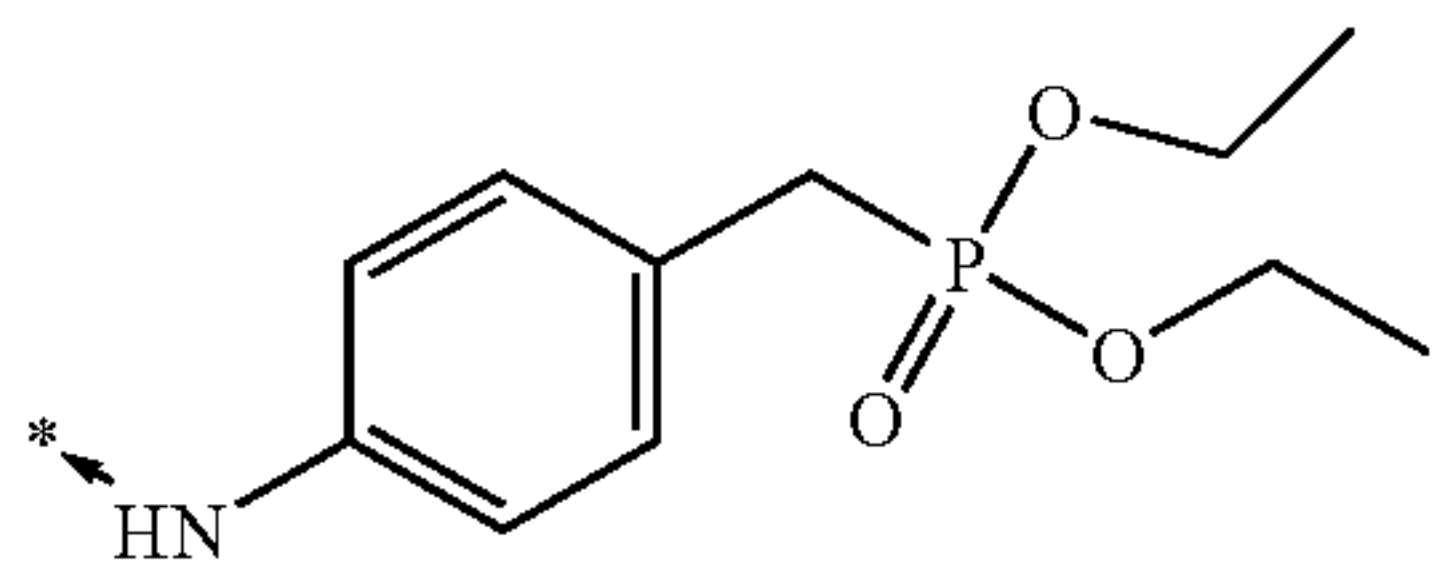
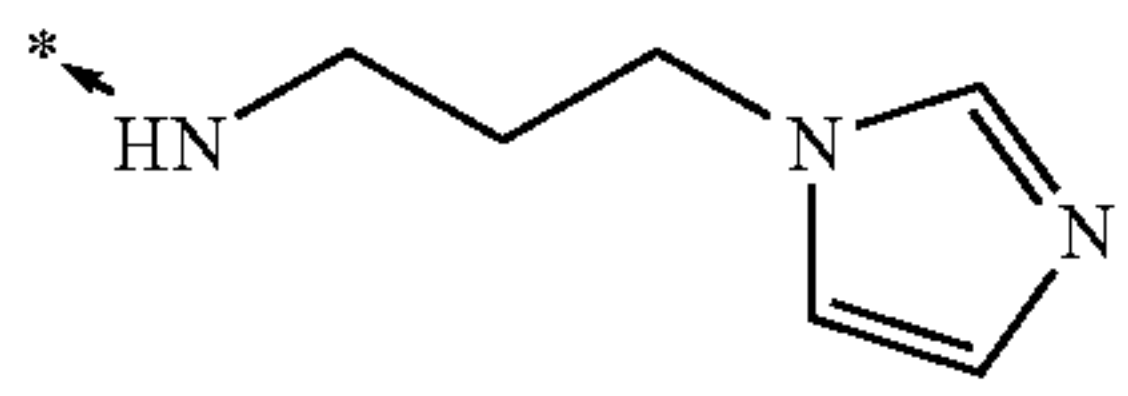
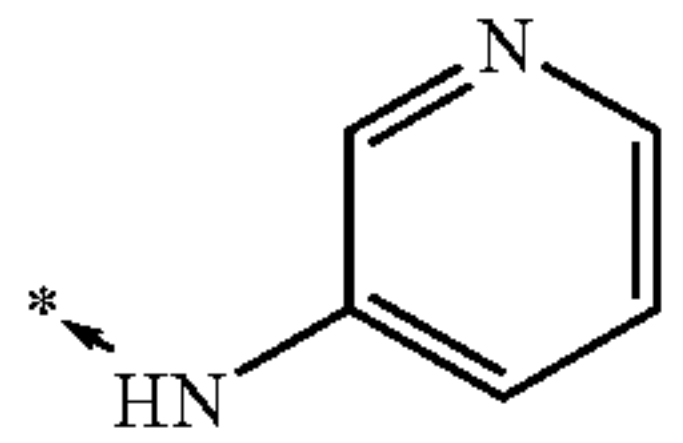
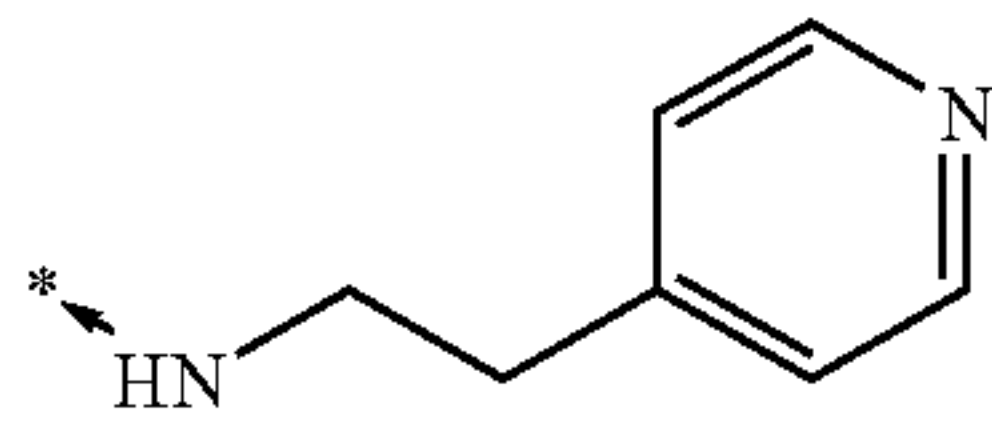
	Example 645 100%, 2.88 min 460(M + 1)	Example 646 94%, 3.59 min 544(M + 1)	Example 647 90%, 3.11 min 520(M + 1)	Example 648 90%, 3.34 min 552(M + 1)
	Example 652 92%, 2.95 min 429(M + 1)	Example 653 89%, 3.67 min 513(M + 1)	Example 654 87%, 3.19 min 489(M + 1)	Example 655 94%, 3.41 min 521(M + 1)
	Example 659 96%, 2.87 min 457(M + 1)	Example 660 89%, 3.58 min 541(M + 1)	Example 661 90%, 3.10 min 517(M + 1)	Example 662 91%, 3.34 min 549(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time

lower line: MS(APCI+, m/e)

TABLE 9-2

basic structure			
			
Rx			
			
Ry			
	Example 642 100%, 3.99 min 714 (M + 1)	Example 643 96%, 4.46 min 660 (M + 1)	Example 644 100%, 4.22 min 646 (M + 1)
	Example 649 100%, 3.20 min 596 (M + 1)	Example 650 93%, 3.55 min 542 (M + 1)	Example 651 100%, 3.32 min 528 (M + 1)
	Example 656 98%, 3.26 min 565 (M + 1)	Example 657 90%, 3.65 min 511 (M + 1)	Example 658 100%, 3.42 min 497 (M + 1)
	Example 663 100%, 3.19 min 593 (M + 1)	Example 664 91%, 3.55 min 539 (M + 1)	Example 665 100%, 3.31 min 525 (M + 1)

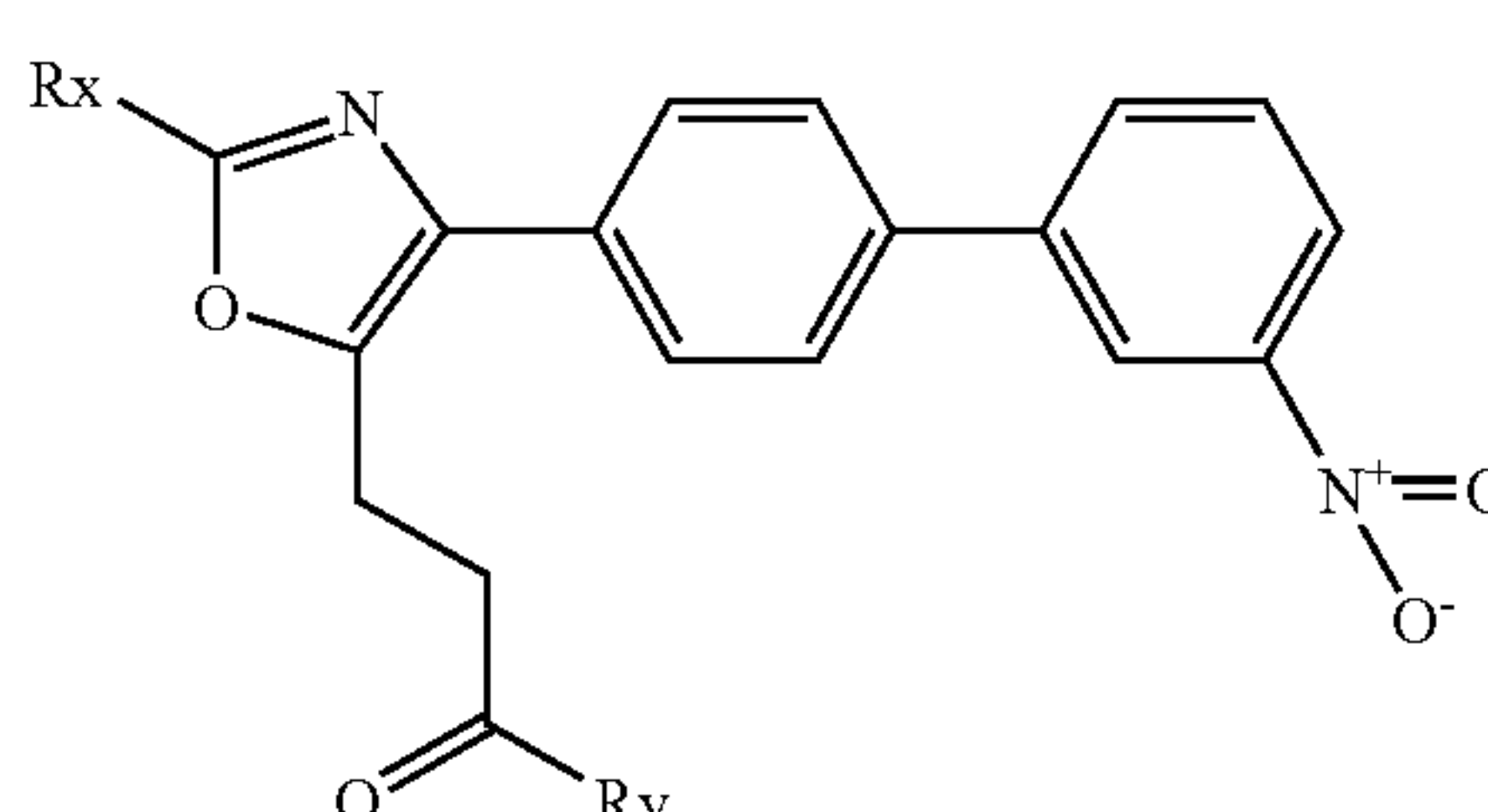
upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

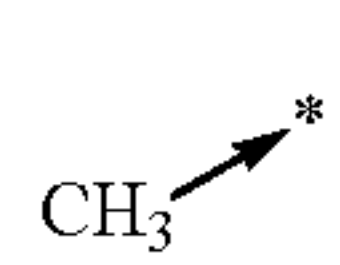
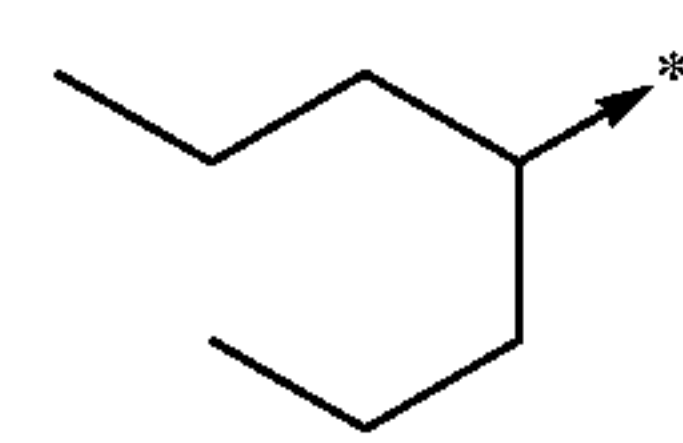
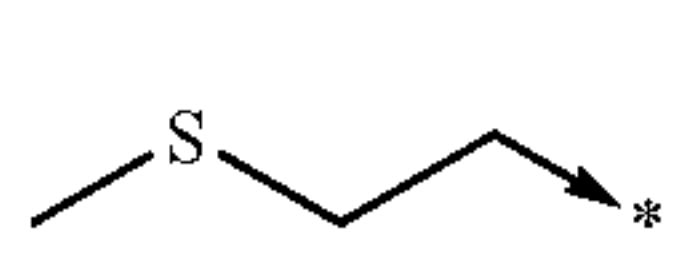
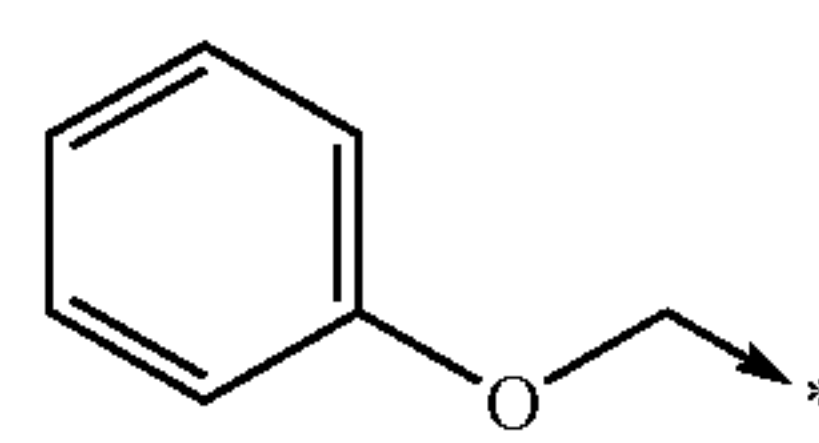
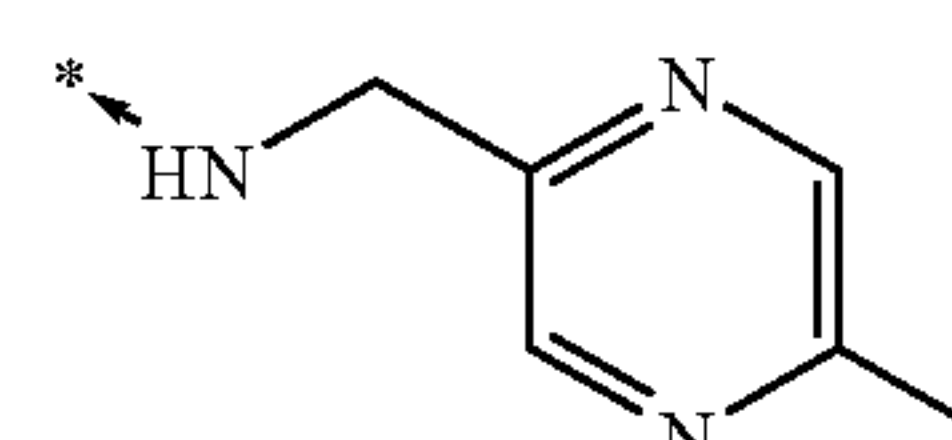
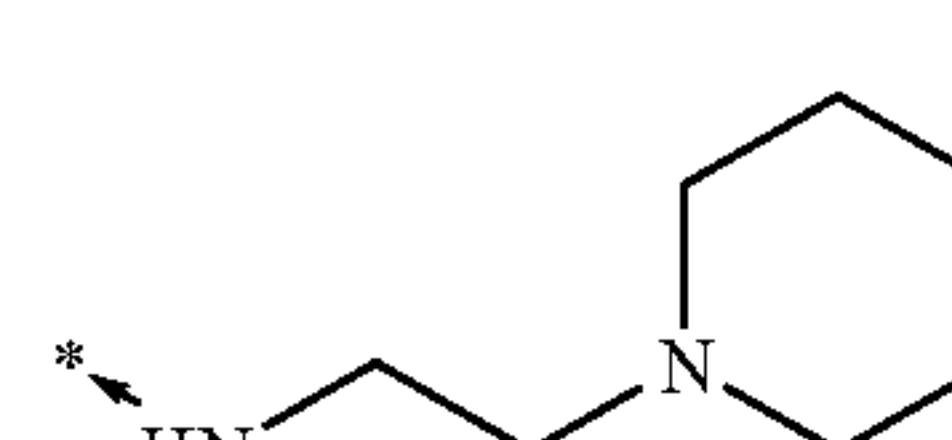
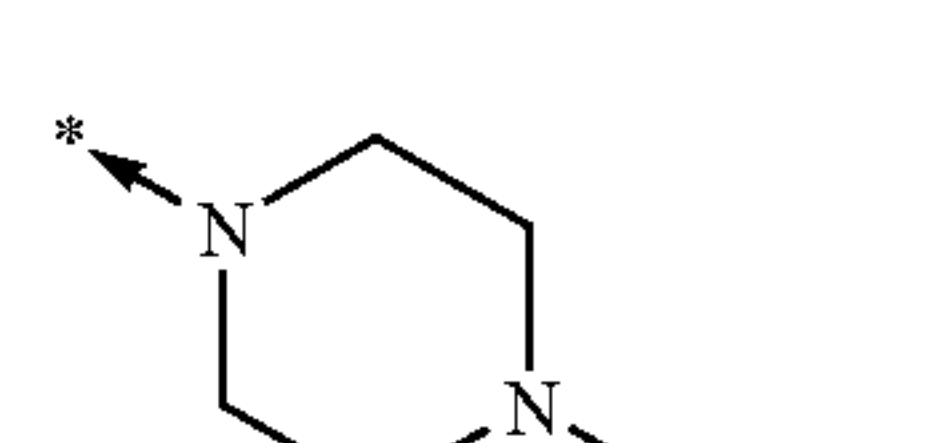
TABLE 9-3

basic structure



Rx

Ry

				
	Example 666 100%, 3.35 min 458 (M + 1)	Example 667 92%, 4.25 min 542 (M + 1)	Example 668 98%, 3.62 min 518 (M + 1)	Example 669 98%, 3.86 min 550 (M + 1)
	Example 673 96%, 2.87 min 465 (M + 1)	Example 674 95%, 3.58 min 549 (M + 1)	Example 675 90%, 3.10 min 525 (M + 1)	Example 676 89%, 3.34 min 557 (M + 1)
	Example 680 95%, 2.86 min 435 (M + 1)	Example 681 92%, 3.59 min 519 (M + 1)	Example 682 92%, 3.10 min 495 (M + 1)	Example 683 90%, 3.35 min 527 (M + 1)

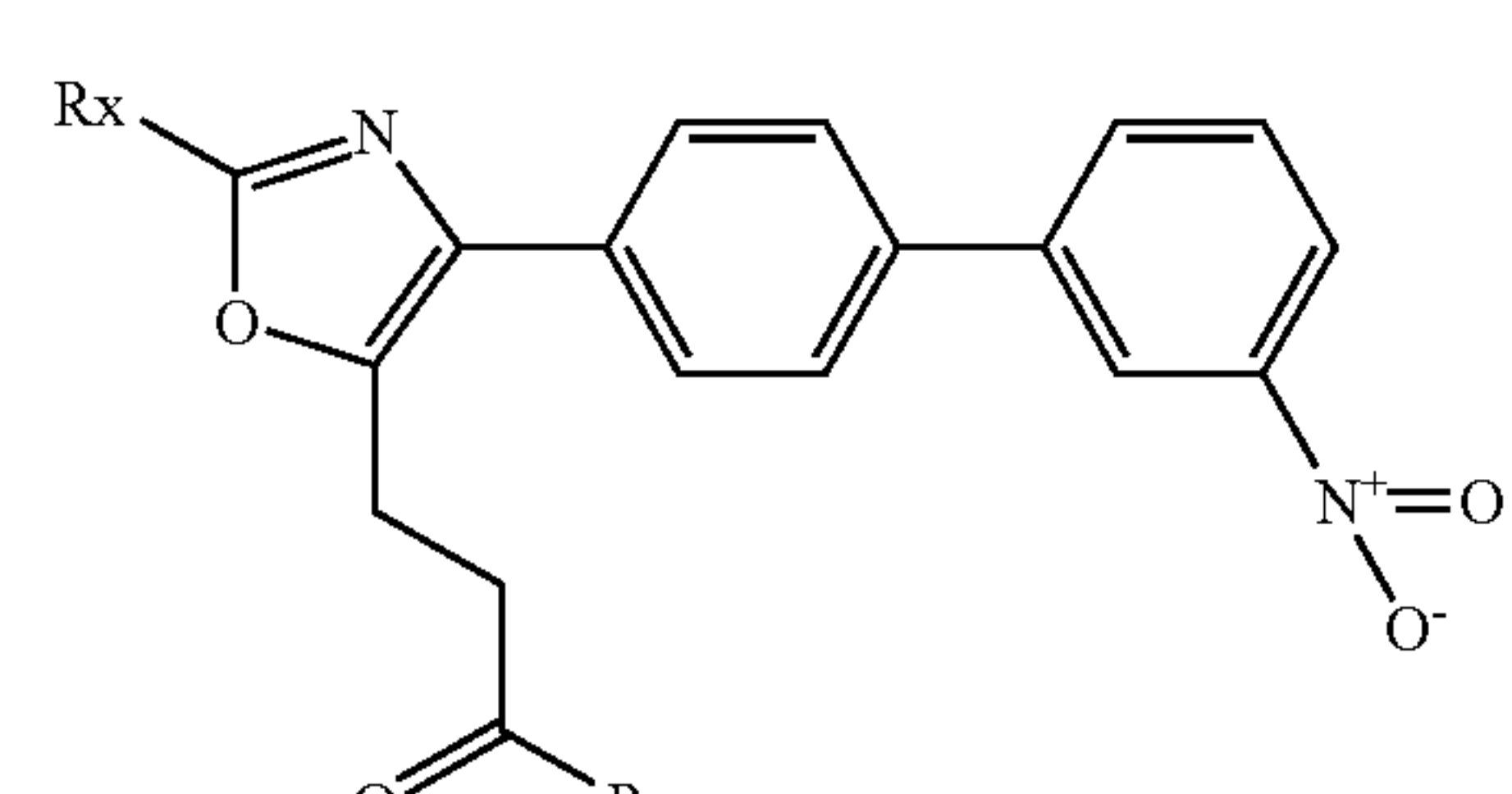
upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 9-4

basic structure



Rx

Ry

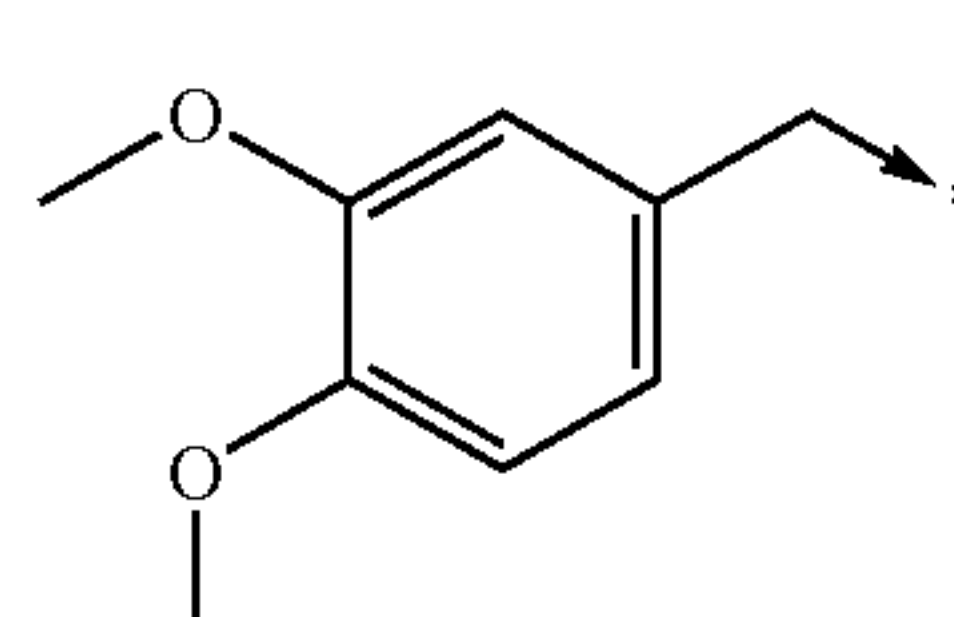
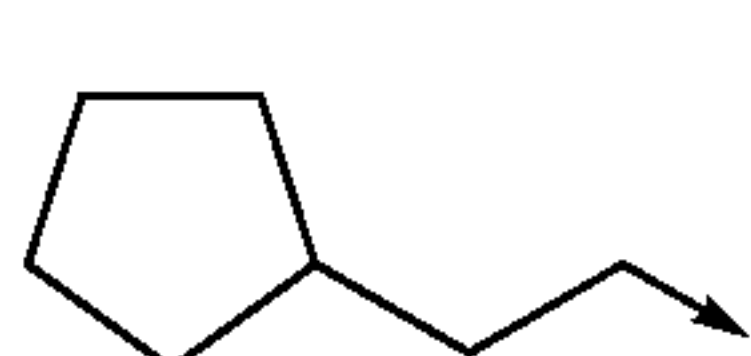
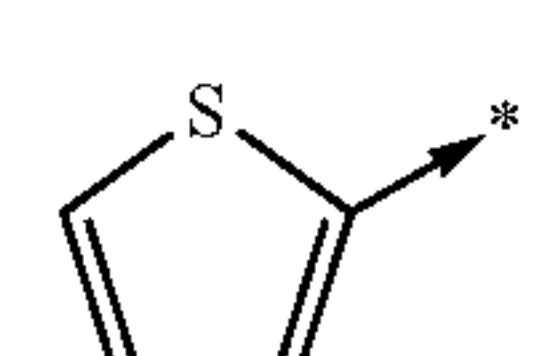
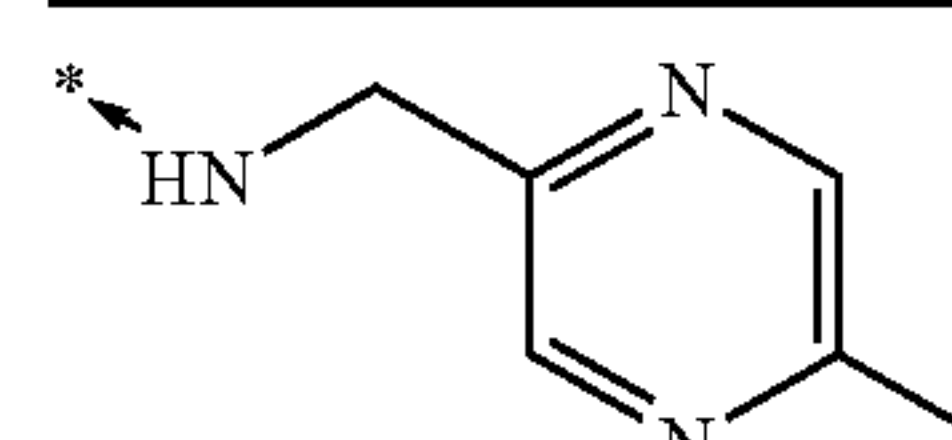
			
	Example 670 100%, 3.68 min 594 (M + 1)	Example 671 97%, 4.20 min 540 (M + 1)	Example 672 97%, 3.88 min 526 (M + 1)

TABLE 9-4-continued

basic structure			
Rx			
Ry			
	<p>Example 677 100%, 3.21 min 601 (M + 1)</p>	<p>Example 678 97%, 3.57 min 547 (M + 1)</p>	<p>Example 679 100%, 3.34 min 533 (M + 1)</p>
	<p>Example 684 100%, 3.20 min 571 (M + 1)</p>	<p>Example 685 90%, 3.56 min 517 (M + 1)</p>	<p>Example 686 100%, 3.34 min 503 (M + 1)</p>

upper line: Example No.
middle line: HPLC purity (220 nm), retention time
lower line: MS (APCI+, m/e)

TABLE 10-1

basic structure				
Rx				
Ry				
	<p>Example 687 94%, 3.60 min 561 (M + 1)</p>	<p>Example 688 86%, 4.33 min 645 (M + 1)</p>	<p>Example 689 94%, 3.81 min 621 (M + 1)</p>	<p>Example 690 95%, 4.02 min 653 (M + 1)</p>
	<p>Example 694 96%, 2.70 min 443 (M + 1)</p>	<p>Example 695 99%, 3.43 min 527 (M + 1)</p>	<p>Example 696 96%, 2.94 min 503 (M + 1)</p>	<p>Example 697 96%, 3.20 min 535 (M + 1)</p>

TABLE 10-1-continued

basic structure				
Rx				
Ry				
	Example 701 97%, 2.77 min 412 (M + 1)	Example 702 95%, 3.52 min 496 (M + 1)	Example 703 88%, 3.01 min 472 (M + 1)	Example 704 96%, 3.26 min 504 (M + 1)
	Example 708 97%, 2.69 min 440 (M + 1)	Example 709 97%, 3.43 min 524 (M + 1)	Example 710 94%, 2.93 min 500 (M + 1)	Example 711 96%, 3.18 min 532 (M + 1)

upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 10-2

basic structure			
Rx			
Ry			
	Example 691 91%, 3.85 min 697 (M + 1)	Example 692 95%, 4.30 min 643 (M + 1)	Example 693 100%, 4.05 min 629 (M + 1)

TABLE 10-2-continued

basic structure				
Rx				
Ry				
	Example 698 96%, 3.04 min 579 (M + 1)	Example 699 100%, 3.42 min 525 (M + 1)	Example 700 98%, 3.16 min 511 (M + 1)	
	Example 705 92%, 3.10 min 548 (M + 1)	Example 706 99%, 3.49 min 494 (M + 1)	Example 707 84%, 3.27 min 480 (M + 1)	
	Example 712 93%, 3.04 min 576 (M + 1)	Example 713 100%, 3.41 min 522 (M + 1)	Example 714 91%, 3.14 min 508 (M + 1)	

upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 10-3

basic structure				
Rx				
Ry				
	Example 715 95%, 3.13 min 441 (M + 1)	Example 716 97%, 4.05 min 525 (M + 1)	Example 717 88%, 3.43 min 501 (M + 1)	Example 718 92%, 3.70 min 533 (M + 1)

TABLE 10-3-continued

basic structure				
Rx				
Ry				
	Example 722 91%, 2.70 min 448 (M + 1)	Example 723 100%, 3.45 min 532 (M + 1)	Example 724 95%, 2.95 min 508 (M + 1)	Example 725 97%, 3.22 min 540 (M + 1)
	Example 729 92%, 2.70 min 418 (M + 1)	Example 730 97%, 3.45 min 502 (M + 1)	Example 731 94%, 2.95 min 478 (M + 1)	Example 732 93%, 3.22 min 510 (M + 1)

upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 10-4

basic structure			
Rx			
Ry			
	Example 719 97%, 3.49 min 577 (M + 1)	Example 720 100%, 4.01 min 523 (M + 1)	Example 721 100%, 3.68 min 509 (M + 1)
	Example 726 100%, 3.06 min 584 (M + 1)	Example 727 99%, 3.43 min 530 (M + 1)	Example 728 94%, 3.17 min 516 (M + 1)

TABLE 10-4-continued

basic structure			
Rx			
Ry			
	Example 733 95%, 3.06 min 554 (M + 1)	Example 734 91%, 3.43 min 500 (M + 1)	Example 735 93%, 3.18 min 486 (M + 1)

upper line: Example No.
 middle line: HPLC purity (220 nm), retention time
 lower line: MS (APCI+, m/e)

TABLE 11-1

basic structure				
Rx				
Ry				
	Example 736 96%, 3.76 min 563 (M + 1)	Example 737 96%, 4.48 min 647 (M + 1)	Example 738 96%, 3.98 min 623 (M + 1)	Example 739 100%, 4.17 min 655 (M + 1)
	Example 743 98%, 2.86 min 445 (M + 1)	Example 744 98%, 3.56 min 529 (M + 1)	Example 745 100%, 3.09 min 505 (M + 1)	Example 746 100%, 3.34 min 537 (M + 1)
	Example 750 100%, 2.94 min 414 (M + 1)	Example 751 88%, 3.66 min 498 (M + 1)	Example 752 98%, 3.26 min 474 (M + 1)	Example 753 96%, 3.49 min 506 (M + 1)

TABLE 11-1-continued

basic structure				
Rx				
Ry				
	<p>Example 757 99%, 2.85 min 442 (M + 1)</p>	<p>Example 758 98%, 3.56 min 526 (M + 1)</p>	<p>Example 759 98%, 3.09 min 502 (M + 1)</p>	<p>Example 760 100%, 3.33 min 534 (M + 1)</p>

upper line:
Example No.
middle line:
HPLC purity (220 nm), retention time
lower line:
MS (APCI+, m/e)

TABLE 11-2

basic structure			
Rx			
Ry			
	<p>Example 740 100%, 4.00 min 699 (M + 1)</p>	<p>Example 741 99%, 4.45 min 645 (M + 1)</p>	<p>Example 742 100%, 4.21 min 631 (M + 1)</p>
	<p>Example 747 100%, 3.19 min 581 (M + 1)</p>	<p>Example 748 86%, 3.54 min 527 (M + 1)</p>	<p>Example 749 100%, 3.31 min 513 (M + 1)</p>

TABLE 11-2-continued

basic structure				
Rx				
Ry				
	Example 754	Example 755	Example 756	
	99%, 3.28 min	95%, 3.65 min	99%, 3.42 min	
	550 (M + 1)	496 (M + 1)	482 (M + 1)	
	Example 761	Example 762	Example 763	
	100%, 3.18 min	87%, 3.54 min	99%, 3.28 min	
	578 (M + 1)	524 (M + 1)	510 (M + 1)	

upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 11-3

basic structure				
Rx				
Ry				
	Example 764	Example 765	Example 766	Example 767
	96%, 3.33 min	84%, 4.22 min	100%, 3.61 min	100%, 3.88 min
	443 (M + 1)	527 (M + 1)	503 (M + 1)	535 (M + 1)
	Example 771	Example 772	Example 773	Example 774
	99%, 2.86 min	93%, 3.58 min	100%, 3.13 min	100%, 3.38 min
	450 (M + 1)	534 (M + 1)	510 (M + 1)	542 (M + 1)

TABLE 11-3-continued

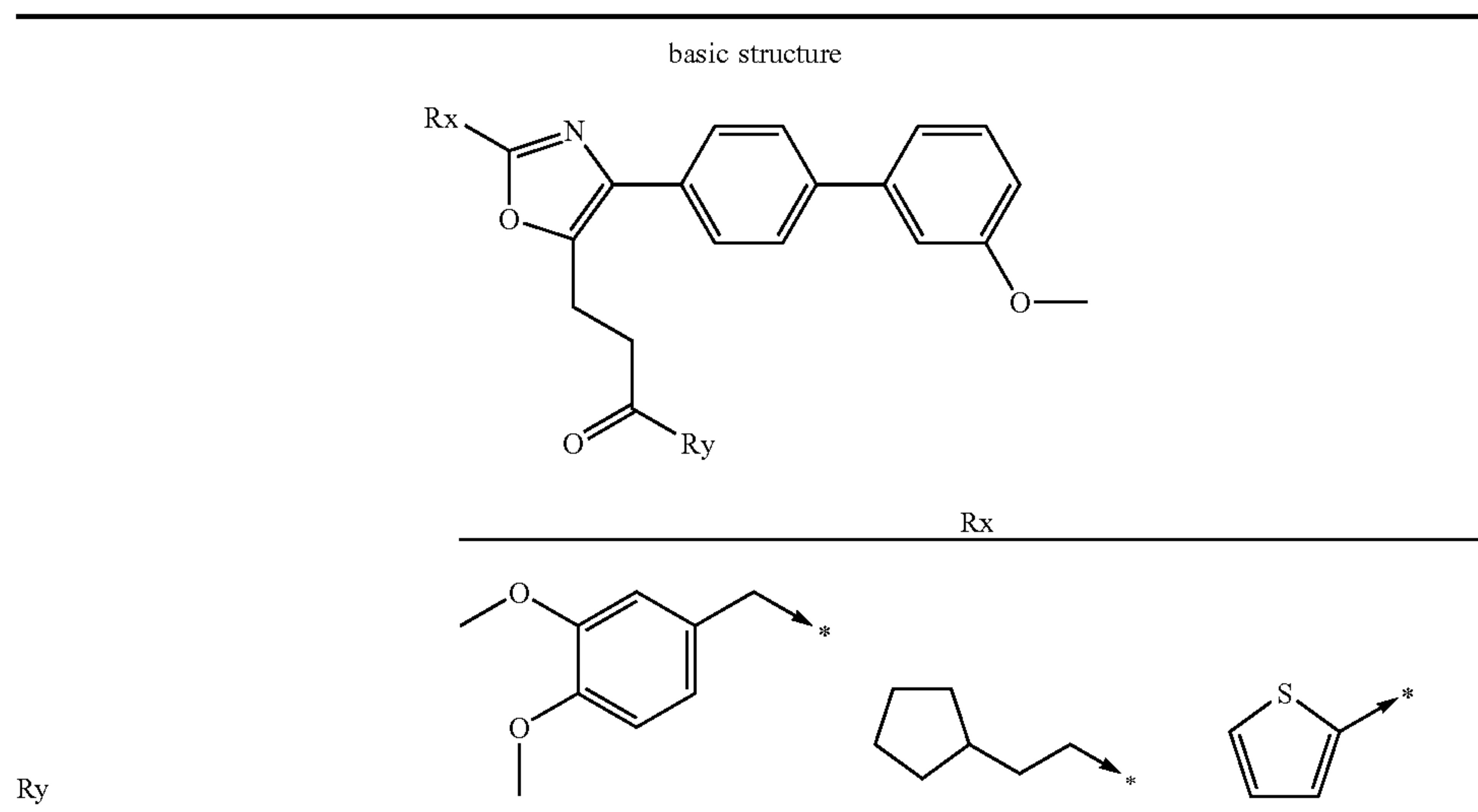
basic structure				
Rx				
Ry				
	Example 778 100%, 2.85 min 420 (M + 1)	Example 779 89%, 3.57 min 504 (M + 1)	Example 780 100%, 3.10 min 480 (M + 1)	Example 781 99%, 3.35 min 512 (M + 1)

upper line: Example No.
 middle line: HPLC purity (220 nm), retention time
 lower line: MS (APCI+, m/e)

TABLE 11-4

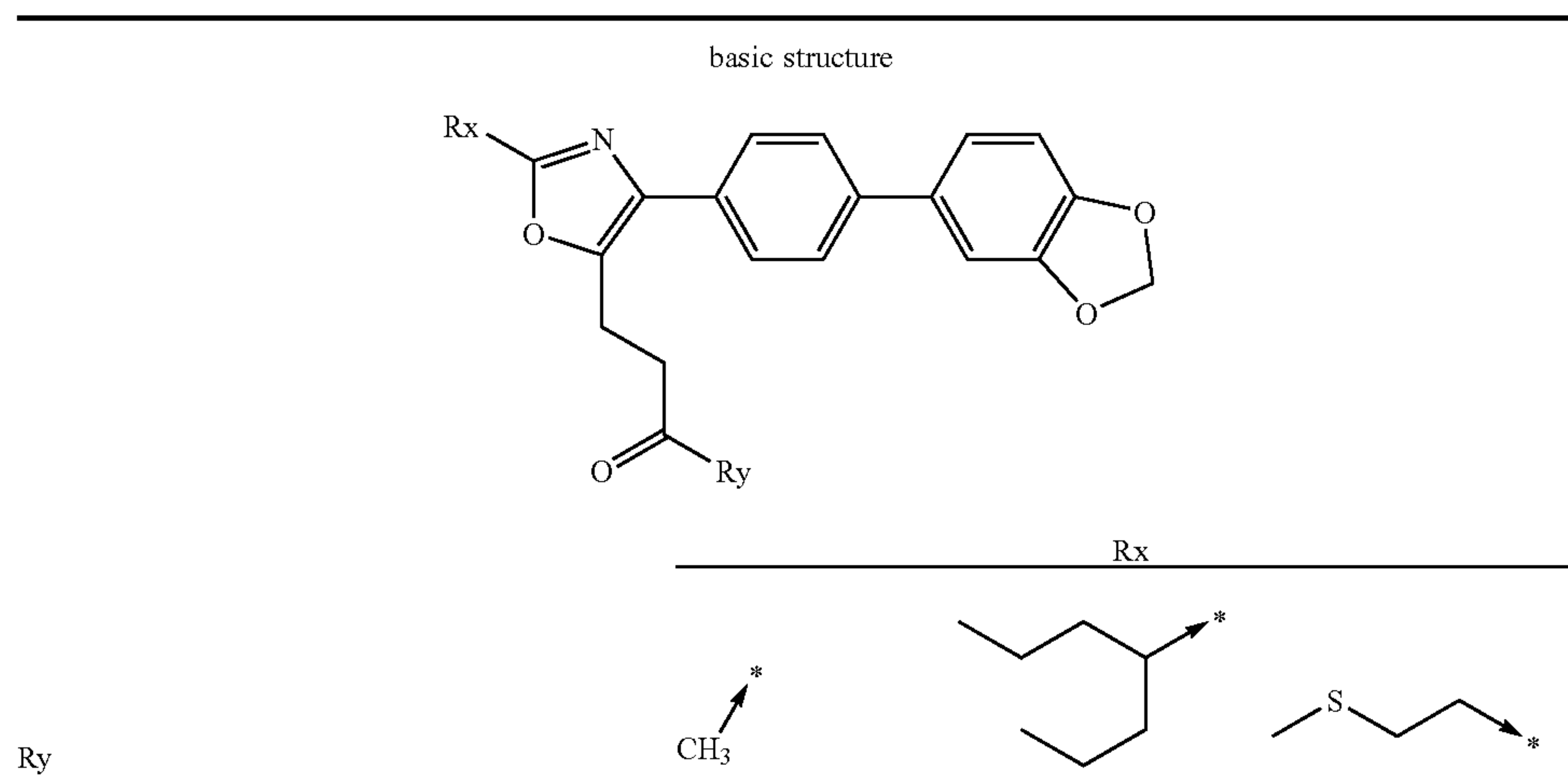
basic structure				
Rx				
Ry				
	Example 768 100%, 3.67 min 579 (M + 1)	Example 769 96%, 4.18 min 525 (M + 1)	Example 770 100%, 3.86 min 511 (M + 1)	
	Example 775 100%, 3.22 min 586 (M + 1)	Example 776 100%, 3.57 min 532 (M + 1)	Example 777 97%, 3.34 min 518 (M + 1)	
	Example 782 98%, 3.20 min 556 (M + 1)	Example 783 97%, 3.56 min 502 (M + 1)	Example 784 98%, 3.33 min 488 (M + 1)	

TABLE 11-4-continued



upper line: Example No.
middle line: HPLC purity (220 nm), retention time
lower line: MS (APCI+, m/e)

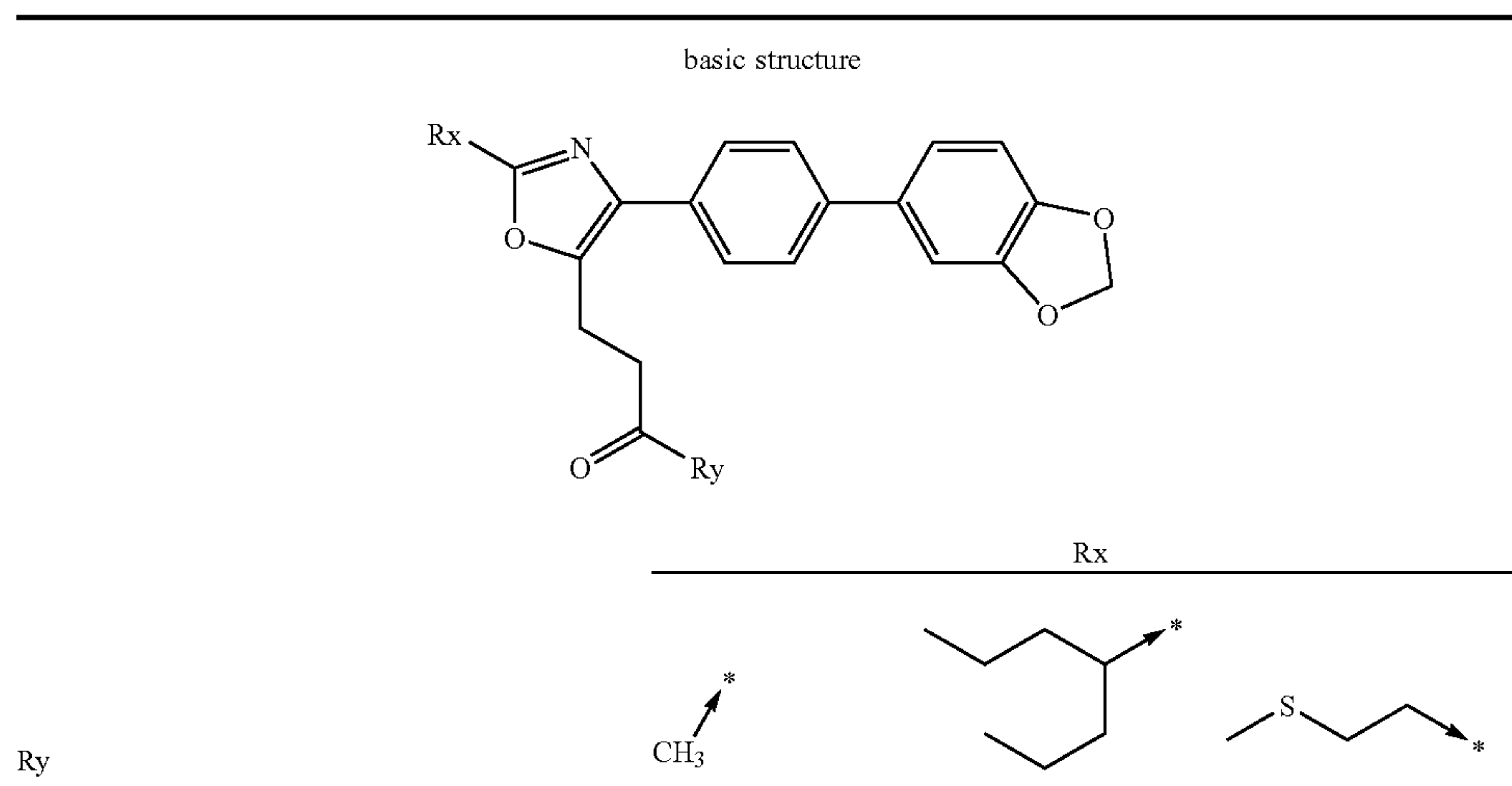
TABLE 12-1



	Example 785 100%, 3.73 min 577 (M + 1)	Example 786 100%, 4.43 min 661 (M + 1)	Example 787 94%, 3.94 min 637 (M + 1)
	Example 791 88%, 2.85 min 459 (M + 1)	Example 792 95%, 3.54 min 543 (M + 1)	
	Example 796 88%, 2.91 min 428 (M + 1)	Example 797 96%, 3.62 min 512 (M + 1)	Example 798 94%, 3.15 min 488 (M + 1)
	Example 800 92%, 2.82 min 456 (M + 1)	Example 801 97%, 3.54 min 540 (M + 1)	

upper line: Example No.

TABLE 12-1-continued



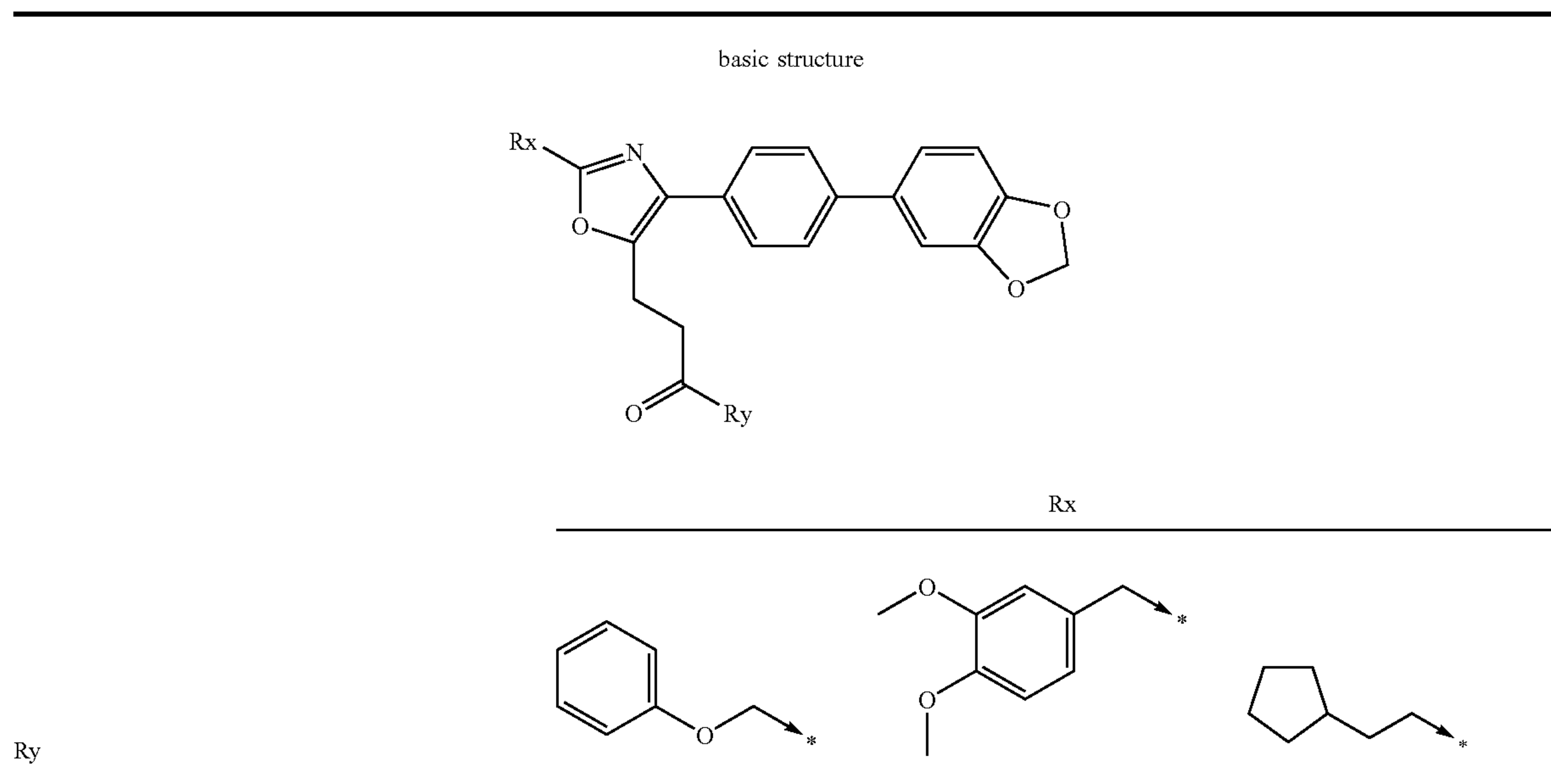
middle line: HPLC purity (220 nm), retention time
 lower line: MS (APCI+, m/e)

TABLE 12-2

basic structure			
Rx			
Ry			
	<p>Example 788 81%, 4.13 min 669 (M + 1)</p>	<p>Example 789 100%, 3.95 min 713 (M + 1)</p>	<p>Example 790 100%, 4.40 min 659 (M + 1)</p>
	<p>Example 793 98%, 3.31 min 551 (M + 1)</p>	<p>Example 794 94%, 3.15 min 595 (M + 1)</p>	<p>Example 795 99%, 3.51 min 541 (M + 1)</p>
			<p>Example 799 99%, 3.60分 510 (M + 1)</p>
	<p>Example 802 95%, 3.30 min 548 (M + 1)</p>	<p>Example 803 94%, 3.14 min 592 (M + 1)</p>	<p>Example 804 99%, 3.51 min 538 (M + 1)</p>

upper line: Example No.

TABLE 12-2-continued



middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 12-3

basic structure			
Rx			
Ry			
	Example 805 100%, 3.29 min 457 (M + 1)	Example 806 91%, 4.17 min 541 (M + 1)	Example 807 100%, 3.57 min 517 (M + 1)
	Example 810 94%, 2.85 min 464 (M + 1)	Example 811 97%, 3.56 min 548 (M + 1)	Example 812 100%, 3.08 min 524 (M + 1)
	Example 815 98%, 2.84 min 434 (M + 1)	Example 816 96%, 3.55 min 518 (M + 1)	Example 817 99%, 3.07 min 494 (M + 1)

upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 12-4

basic structure		
Rx		
Ry		
	<p>Example 808 100%, 3.61 min, 593 (M + 1)</p>	<p>Example 809 96%, 4.12 min 539 (M + 1)</p>
	<p>Example 813 97%, 3.18 min, 600 (M + 1)</p>	<p>Example 814 99%, 3.54 min 546 (M + 1)</p>
	<p>Example 818 96%, 3.17 min 570 (M + 1)</p>	<p>Example 819 98%, 3.55 min 516 (M + 1)</p>

upper line: Example No.
middle line: HPLC purity (220 nm), retention time
lower line: MS (APCI+, m/e)

TABLE 13-1

basic structure				
Rx				
Ry				
	<p>Example 820 100%, 4.09 min 617 (M + 1)</p>	<p>Example 821 100%, 4.75 min 701 (M + 1)</p>	<p>Example 822 100%, 4.26 min 677 (M + 1)</p>	<p>Example 823 100%, 4.43 min 709 (M + 1)</p>

TABLE 13-1-continued

basic structure				
Rx				
Ry				
	<p>Example 827 100%, 3.22 min 499 (M + 1)</p>	<p>Example 828 100%, 3.84 min 583 (M + 1)</p>	<p>Example 829 100%, 3.42 min 559 (M + 1)</p>	<p>Example 830 100%, 3.61 min 591 (M + 1)</p>
	<p>Example 833 100%, 3.31 min 468 (M + 1)</p>	<p>Example 834 100%, 3.93 min 552 (M + 1)</p>	<p>Example 835 90%, 3.53 min 528 (M + 1)</p>	<p>Example 836 100%, 3.73 min 560 (M + 1)</p>
	<p>Example 840 100%, 3.22 min 496 (M + 1)</p>	<p>Example 841 98%, 3.85 min 580 (M + 1)</p>	<p>Example 842 95%, 3.41 min 556 (M + 1)</p>	<p>Example 843 98%, 3.61 min 588 (M + 1)</p>

upper line: Example No.
middle line: HPLC purity (220 nm), retention time
lower line: MS (APCI+, m/e)

TABLE 13-2

basic structure			
Rx			
Ry			
	<p>Example 824 100%, 4.27 min 753 (M + 1)</p>	<p>Example 825 100%, 4.72 min 699 (M + 1)</p>	<p>Example 826 98%, 4.49 min 685 (M + 1)</p>

TABLE 13-2-continued

basic structure			
Rx			
Ry			
	Example 831 100%, 3.48 min 635 (M + 1)	Example 832 100%, 3.80 min 581 (M + 1)	
	Example 837 96%, 3.57 min 604 (M + 1)	Example 838 100%, 3.92 min 550 (M + 1)	Example 839 96%, 3.71 min 536 (M + 1)
	Example 844 100%, 3.47 min 632 (M + 1)	Example 845 96%, 3.83 min 578 (M + 1)	Example 846 100%, 3.59 min 564 (M + 1)

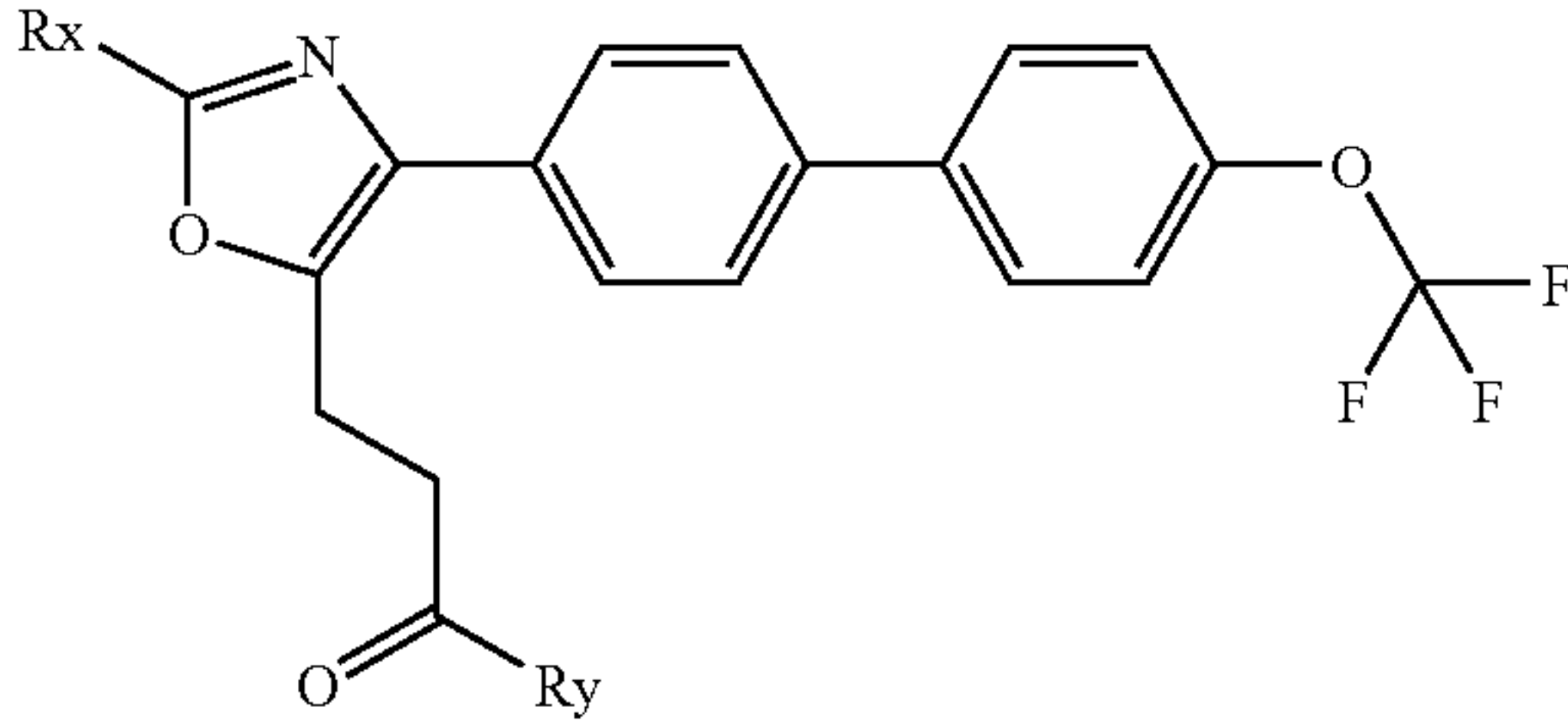
upper line: Example No.
 middle line: HPLC purity (220 nm), retention time
 lower line: MS (APCI+, m/e)

TABLE 13-3

basic structure				
Rx				
Ry				
	Example 847 100%, 3.79 min 497 (M + 1)	Example 848 100%, 4.54 min 581 (M + 1)	Example 849 100%, 3.98 min 557 (M + 1)	Example 850 98%, 4.19 min 589 (M + 1)


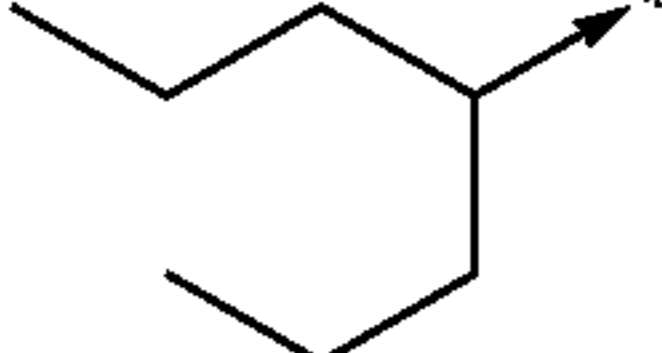
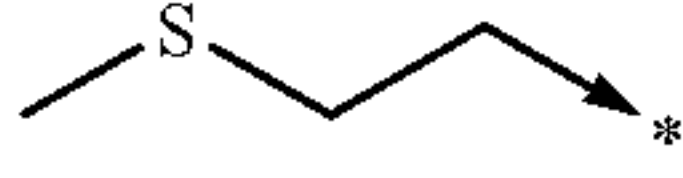
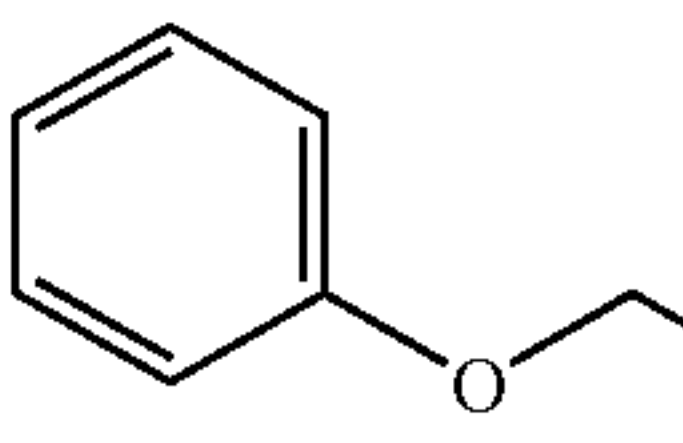
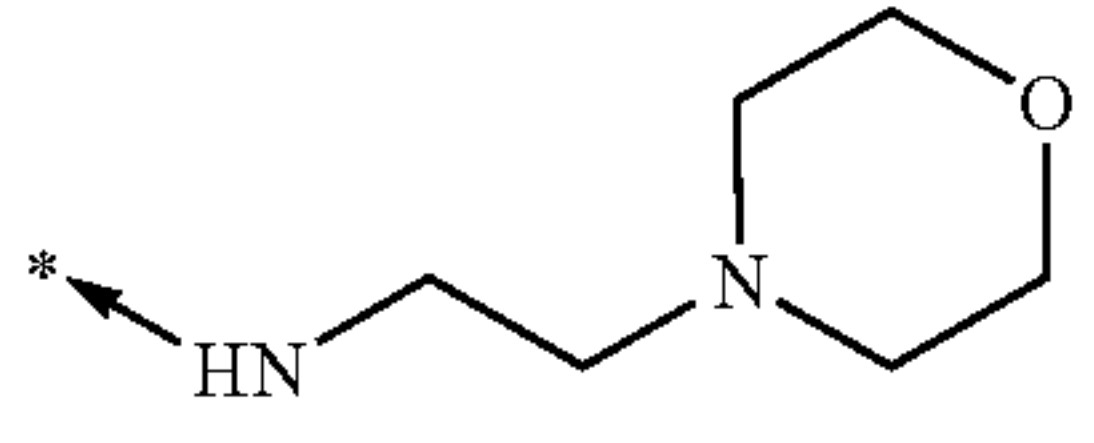
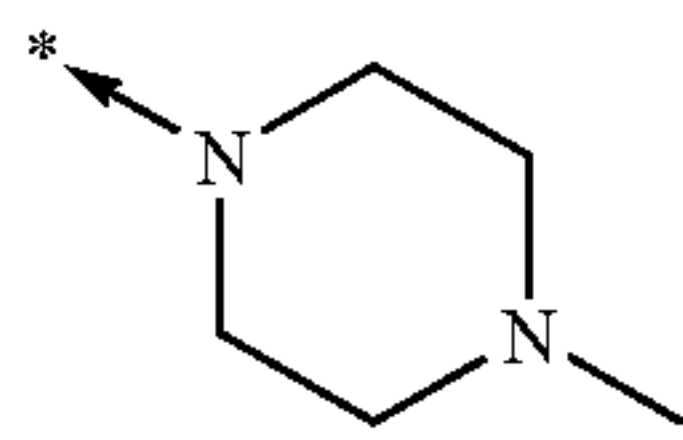
TABLE 13-3-continued

basic structure



Rx

Ry

			
Example 854 100%, 3.24 min 504 (M + 1)	Example 855 97%, 3.87 min 588 (M + 1)	Example 856 97%, 3.43 min 564 (M + 1)	Example 857 99%, 3.64 min 596 (M + 1)
	Example 861 99%, 3.25 min 474 (M + 1)	Example 862 100%, 3.87 min 558 (M + 1)	Example 863 95%, 3.43 min 534 (M + 1)
	Example 864 100%, 3.64 min 566 (M + 1)		

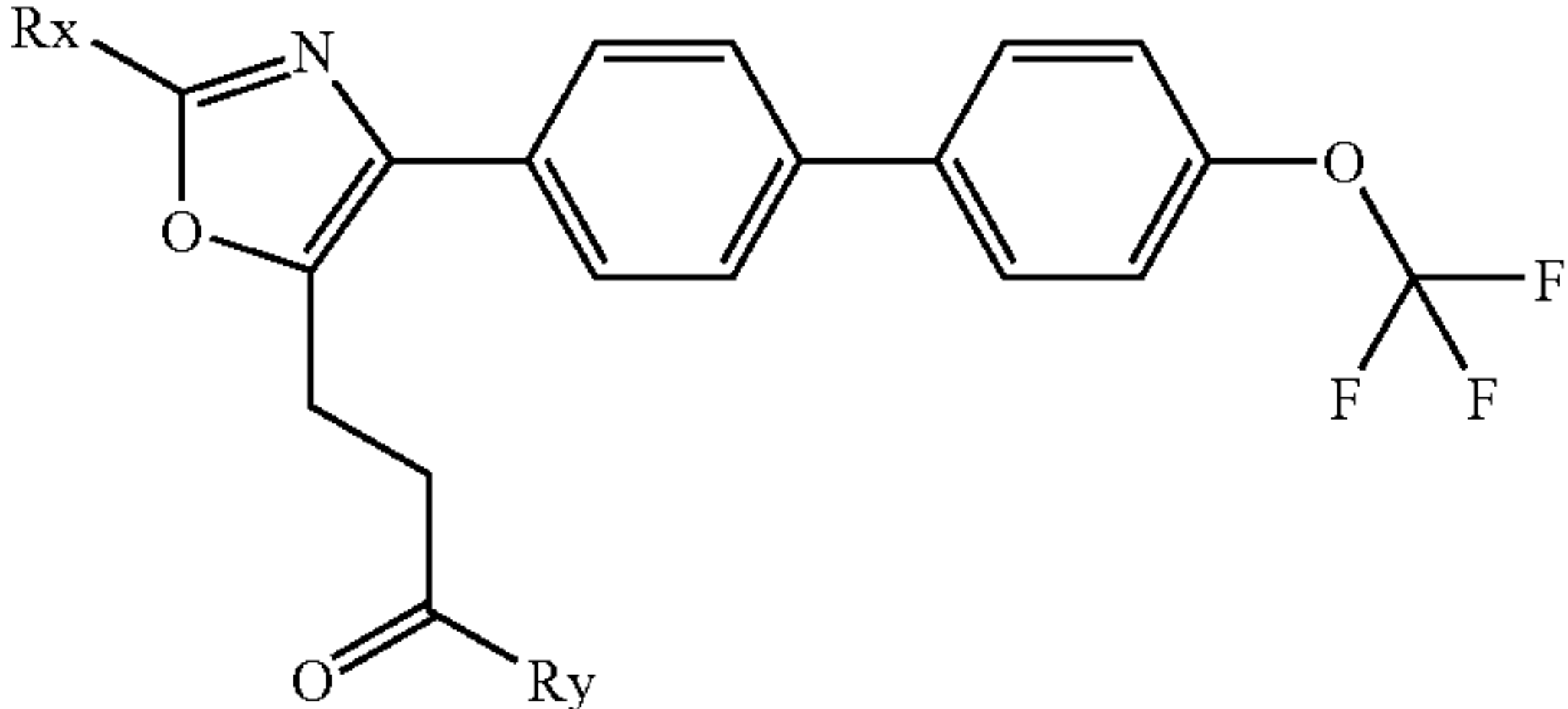
upper line: Example No.

middle line: HPLC purity (220 nm), retention time

lower line: MS (APCI+, m/e)

TABLE 13-4

basic structure



Rx

Ry

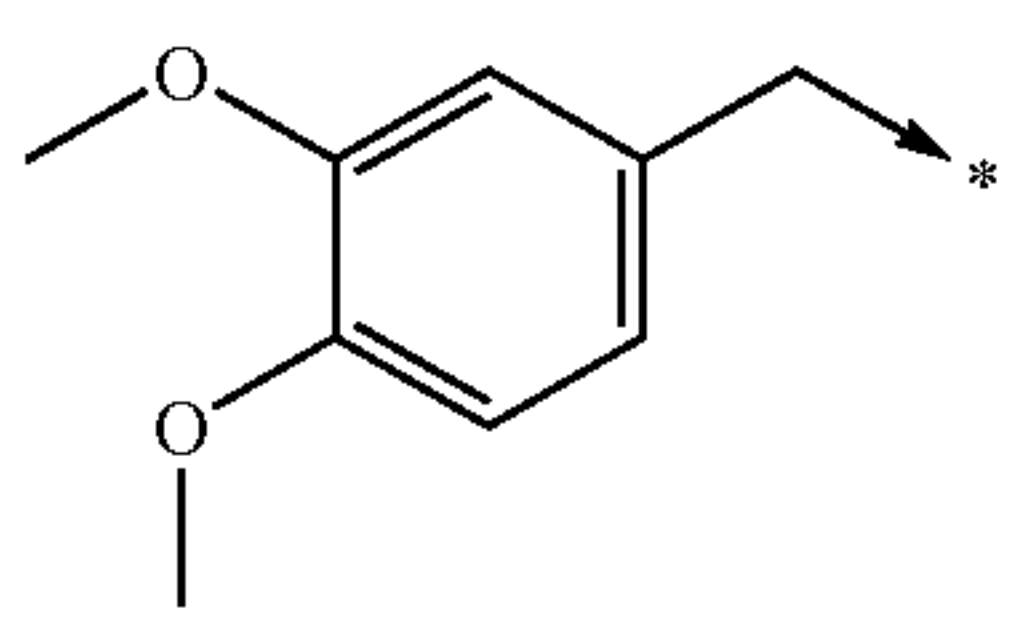
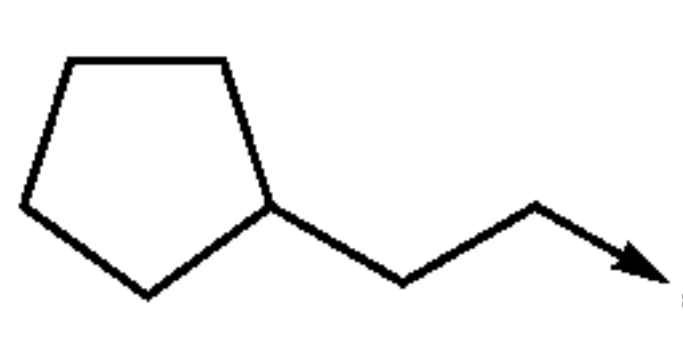
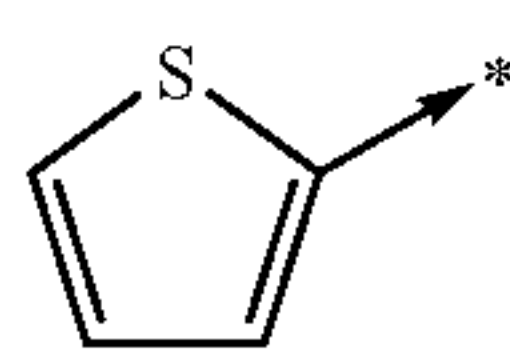
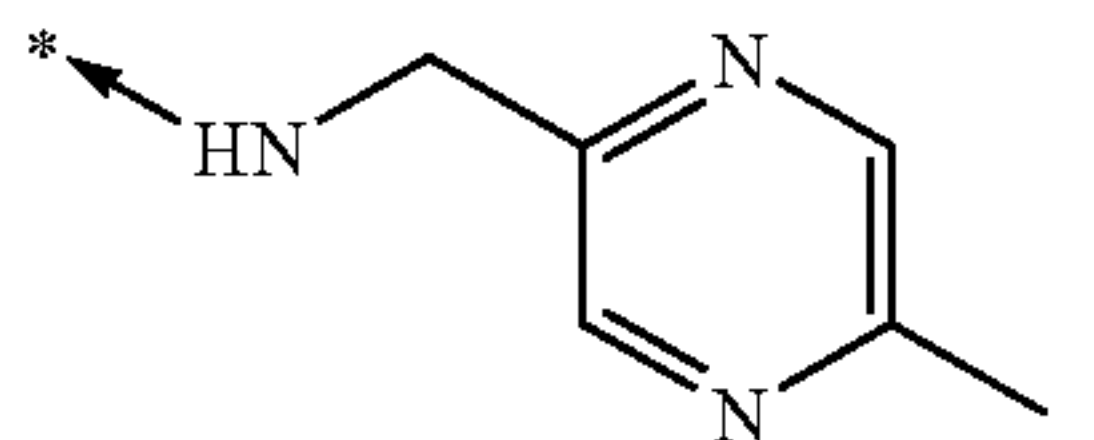
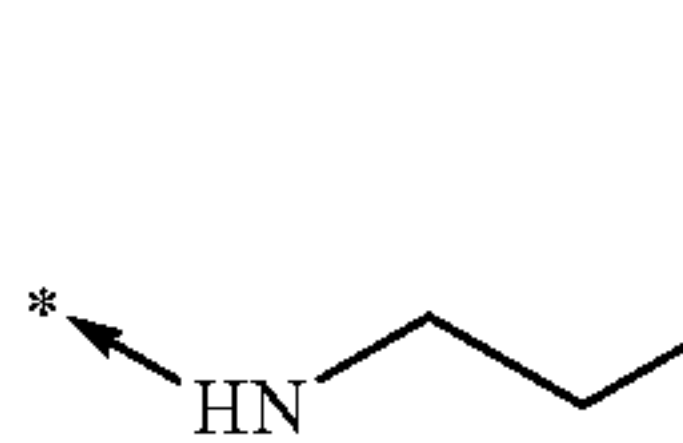
		
Example 851 98%, 4.00 min 633 (M + 1)	Example 852 100%, 4.50 min 579 (M + 1)	Example 853 100%, 4.21 min 565 (M + 1)
	Example 858 99%, 3.50 min 640 (M + 1)	Example 859 98%, 3.84 min 586 (M + 1)
	Example 860 97%, 3.62 min 572 (M + 1)	

TABLE 13-4-continued

basic structure			
Rx			
Ry			
	Example 865 97%, 3.50 min 610 (M + 1)	Example 866 98%, 3.83 min 556 (M + 1)	Example 867 97%, 3.62 min 542 (M + 1)

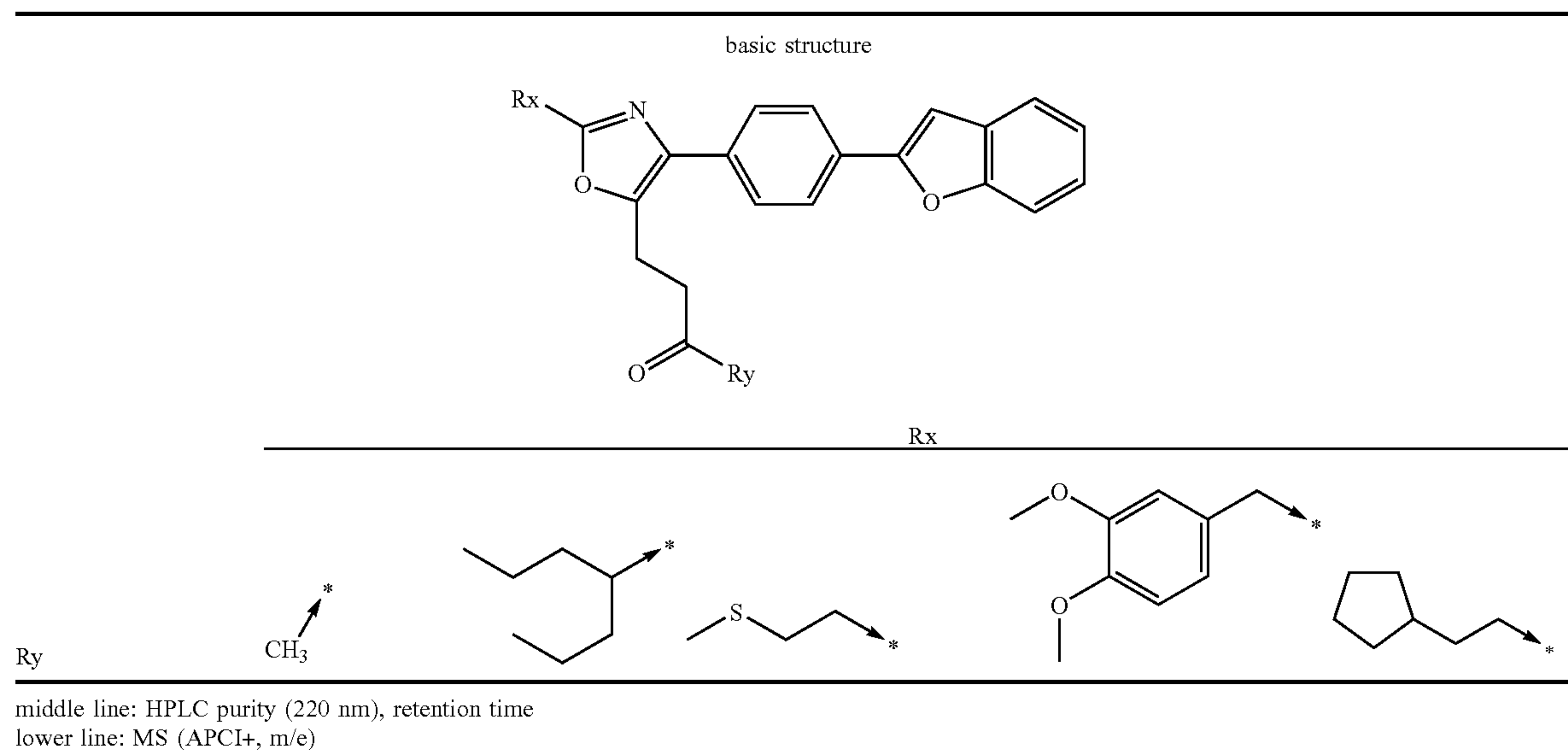
upper line: Example No.
 middle line: HPLC purity (220 nm), retention time
 lower line: MS (APCI+, m/e)

TABLE 14

basic structure					
Rx					
Ry					
	Example 868 92%, 3.33 min 424 (M + 1)	Example 869 83%, 3.53 min 508 (M + 1)	Example 870 100%, 3.49 min 484 (M + 1)	Example 871 100%, 3.54 min 560 (M + 1)	Example 872 90%, 3.52 min 506 (M + 1)
	Example 873 80%, 3.44 min 514 (M + 1)			Example 874 89%, 3.42 min 512 (M + 1)	

upper line: Example No.

TABLE 14-continued



Example 875

25

Examples 876–953

A mixture of diethyl [4-({3-[2-amino-4-(4-chlorophenyl)-1,3-thiazol-5-yl]propanoyl}amino)benzyl]phosphonate (100 mg), ethyl carbamate (50 mg), carbonyldiimidazole (38 mg), diisopropylethylamine (85 μ l) and N,N-dimethylformamide (0.5 ml) was shaken at room temperature for 8 hrs. The reaction mixture was directly poured into preparative HPLC and purified to give the object compound.

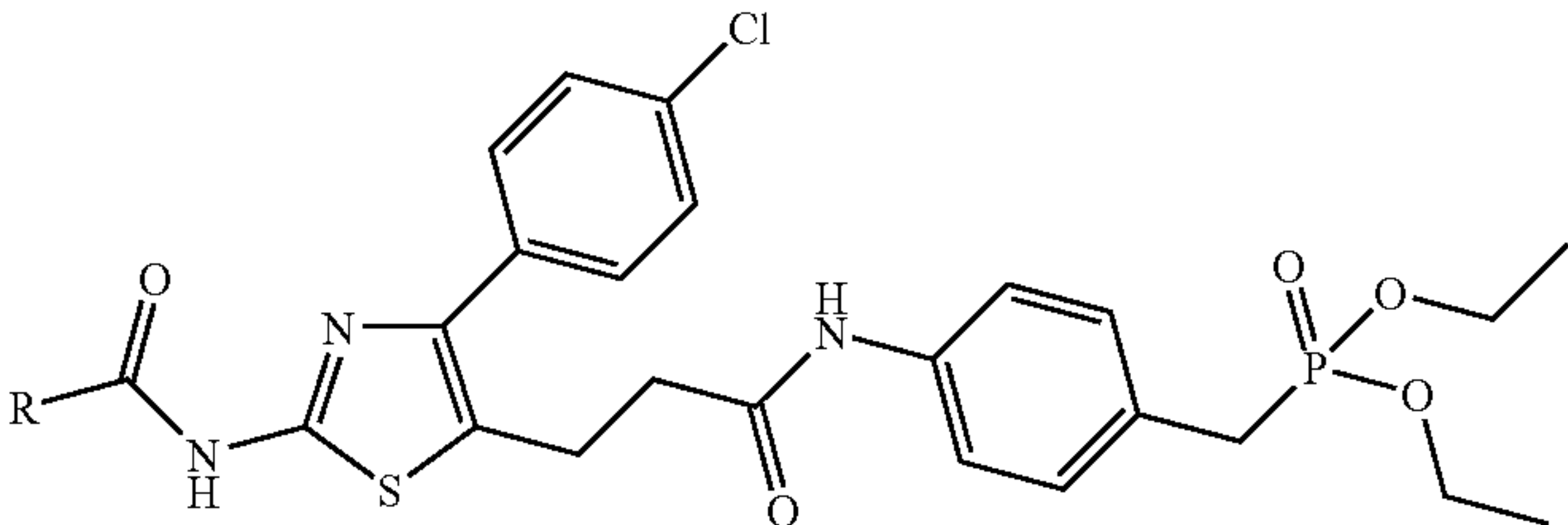
In the same manner as in Example 875, the object compounds were obtained.

The structure and purity of the object compounds of Examples 875–953 were confirmed by LC-MS, HPLC. The yield, structure, purity and mass spectrum data of the object compounds are shown in [Table 15-1]–[Table 15-4], [Table 16-1]–[Table 16-4] and [Table 17].

TABLE 15-1

basic structure				
R				
Example 875 99%, 3.845 667(M + 1)	Example 876 99%, 4.008 661(M + 1)	Example 877 95%, 4.097 619(M + 1)	Example 878 99%, 4.095 659(M + 1)	Example 879 99%, 4.281 645(M + 1)
R				

TABLE 15-1-continued

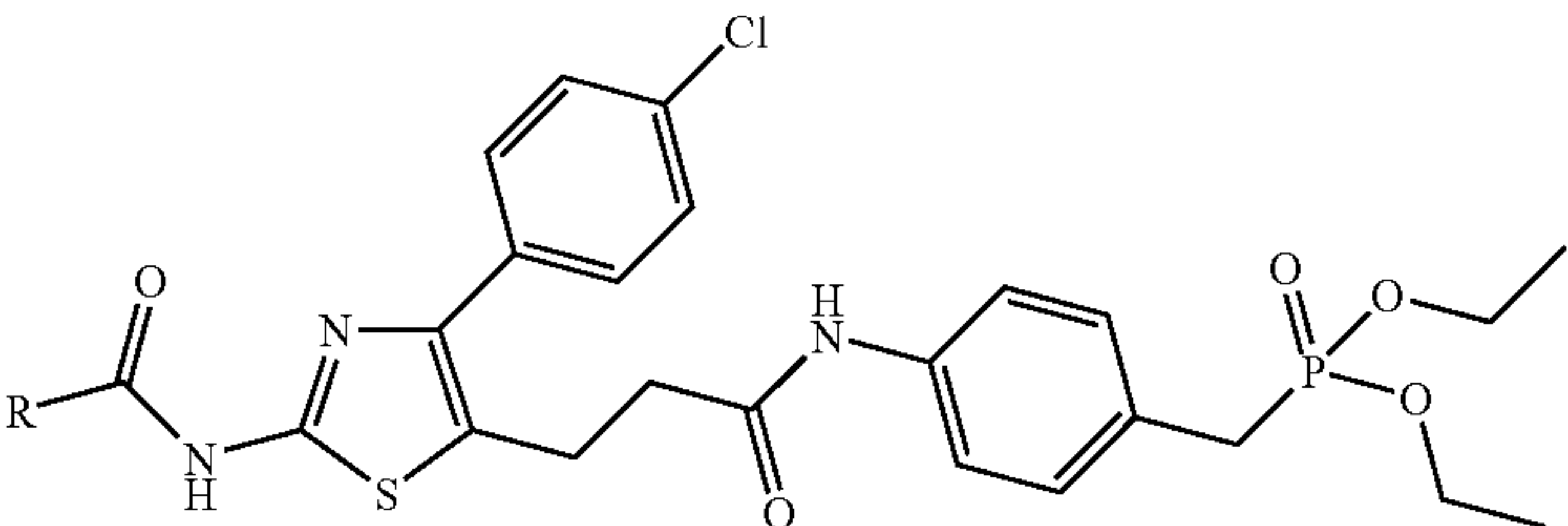
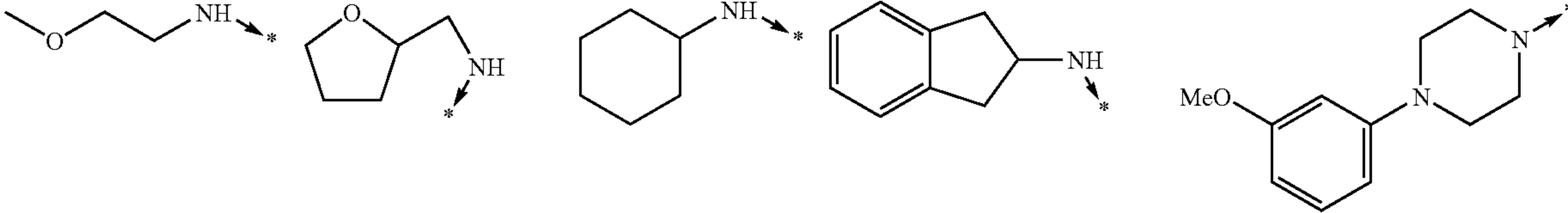
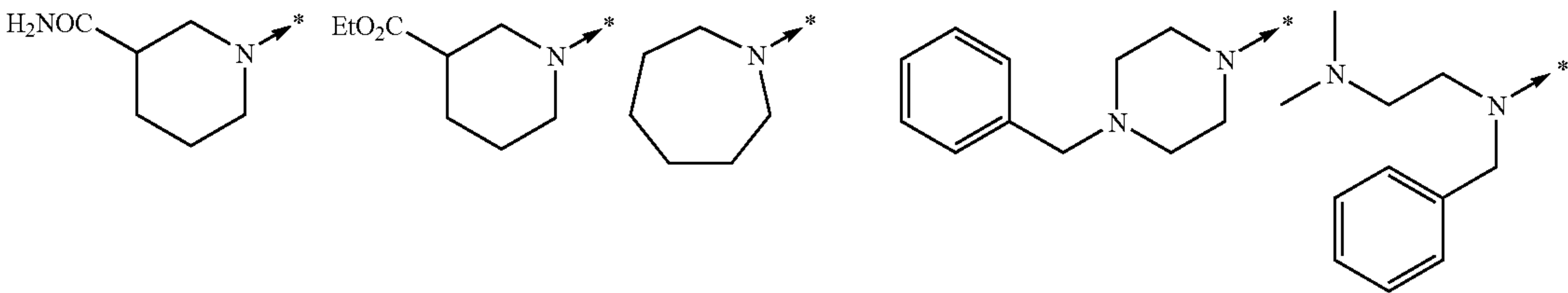
basic structure				
				
Example 880	Example 881	Example 882	Example 883	Example 884
96%, 4.363	93%, 4.027	94%, 4.280	97%, 4.117	99%, 4.386
667(M + 1)	637(M + 1)	655(M + 1)	691(M + 1)	647(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 15-2

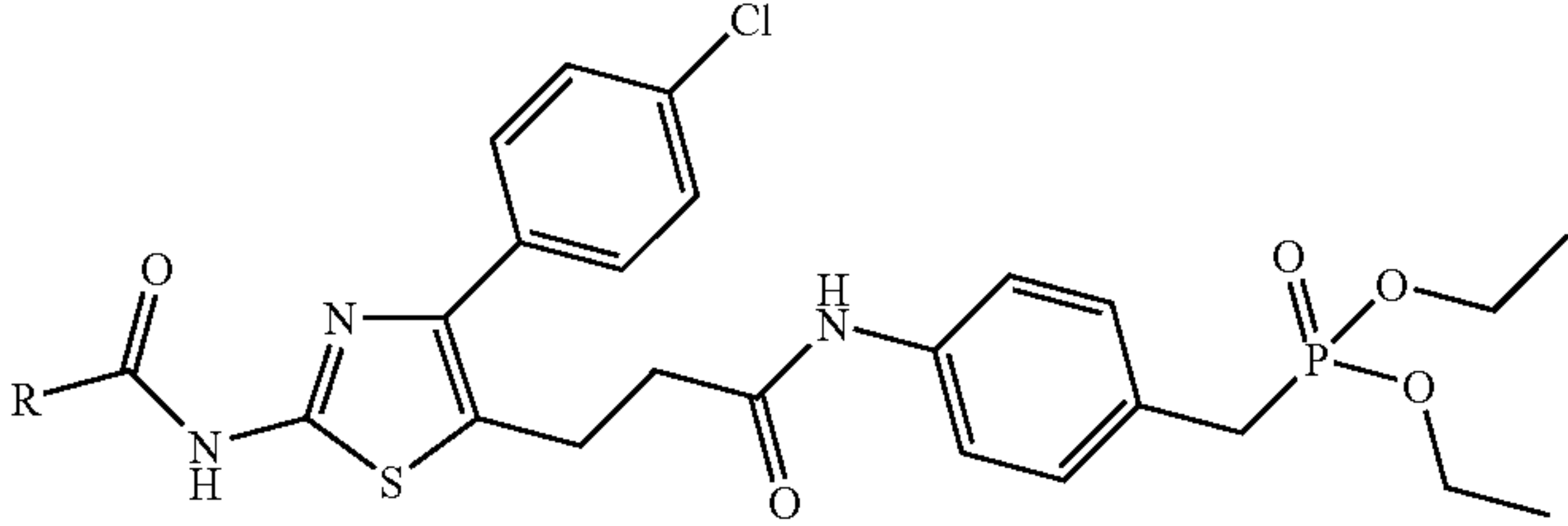
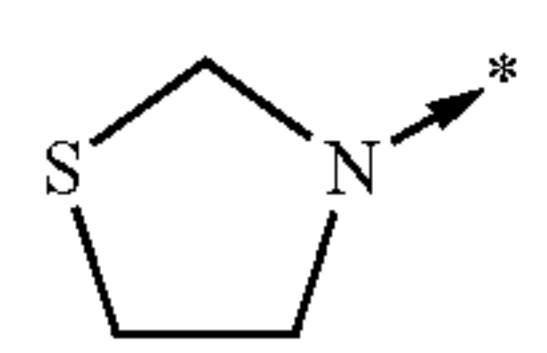
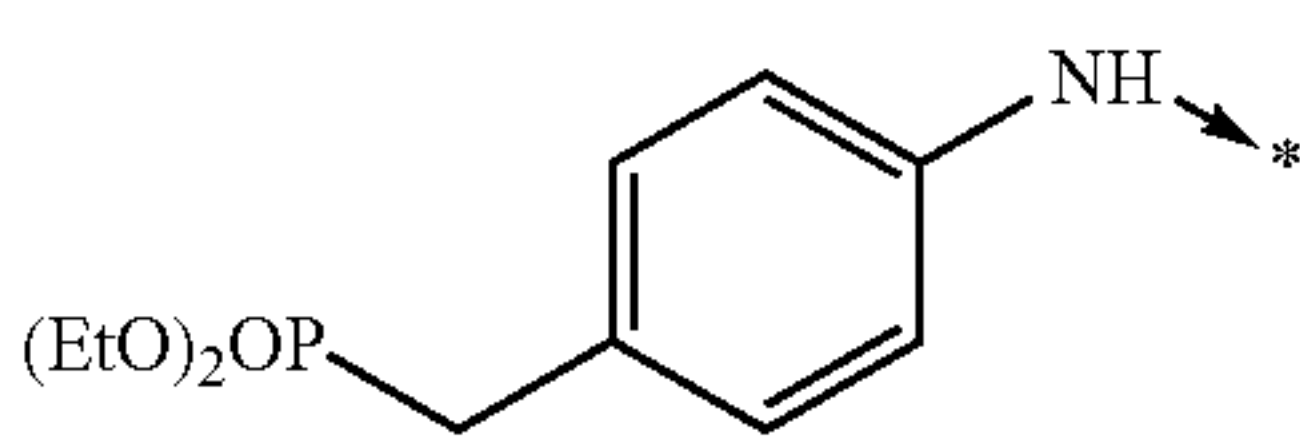
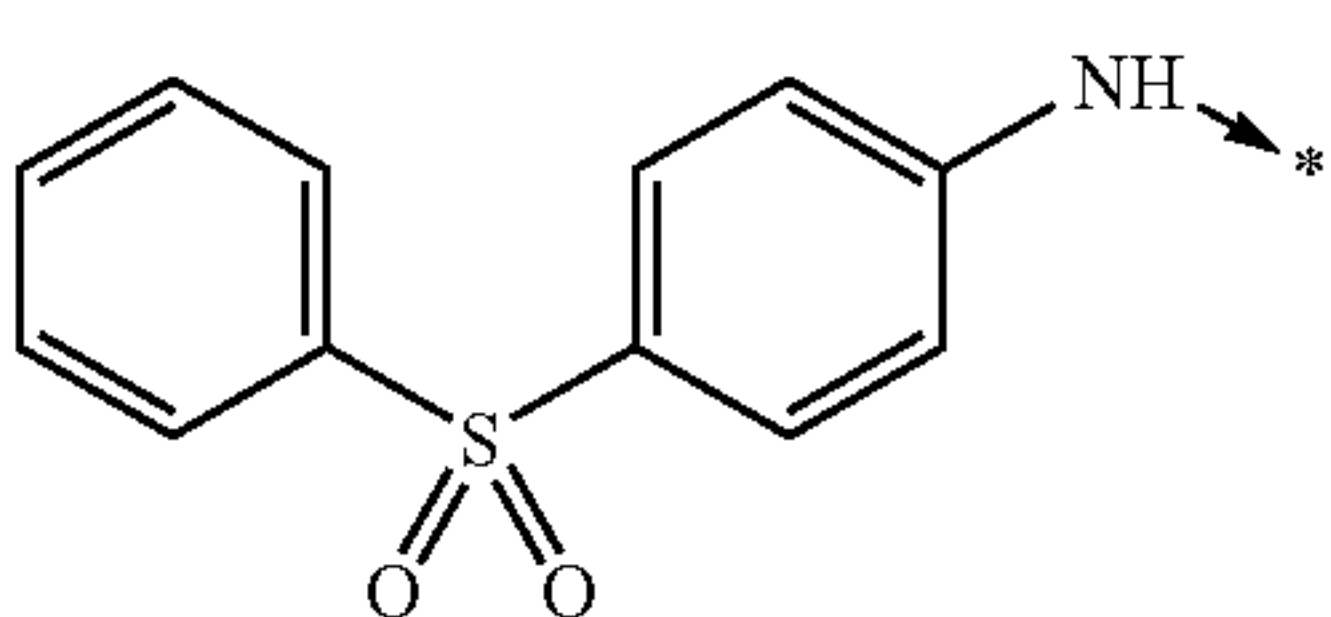
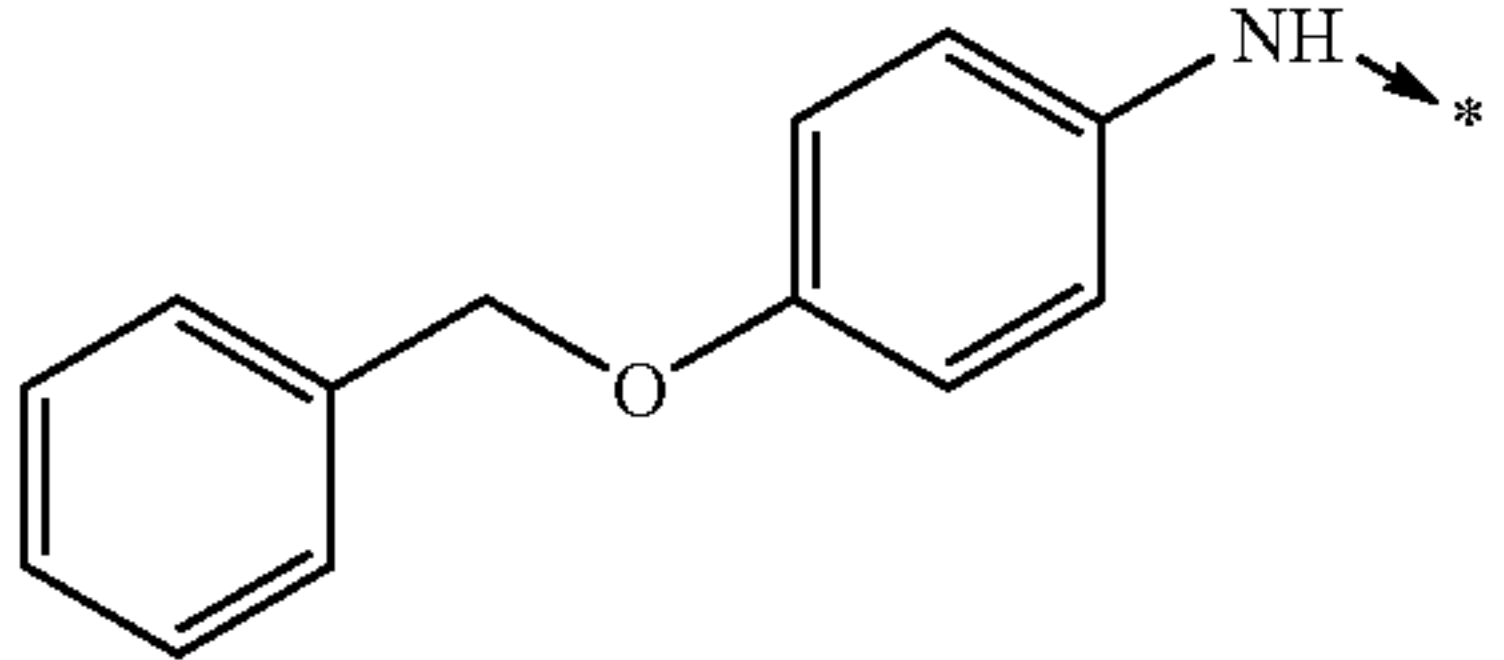
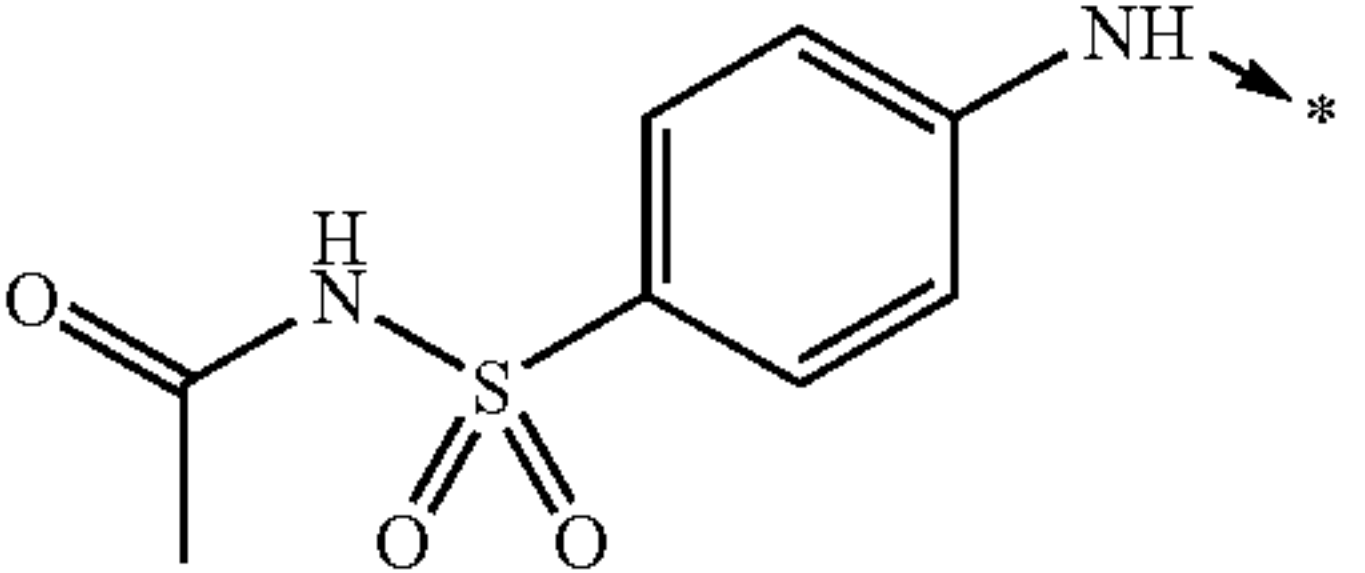
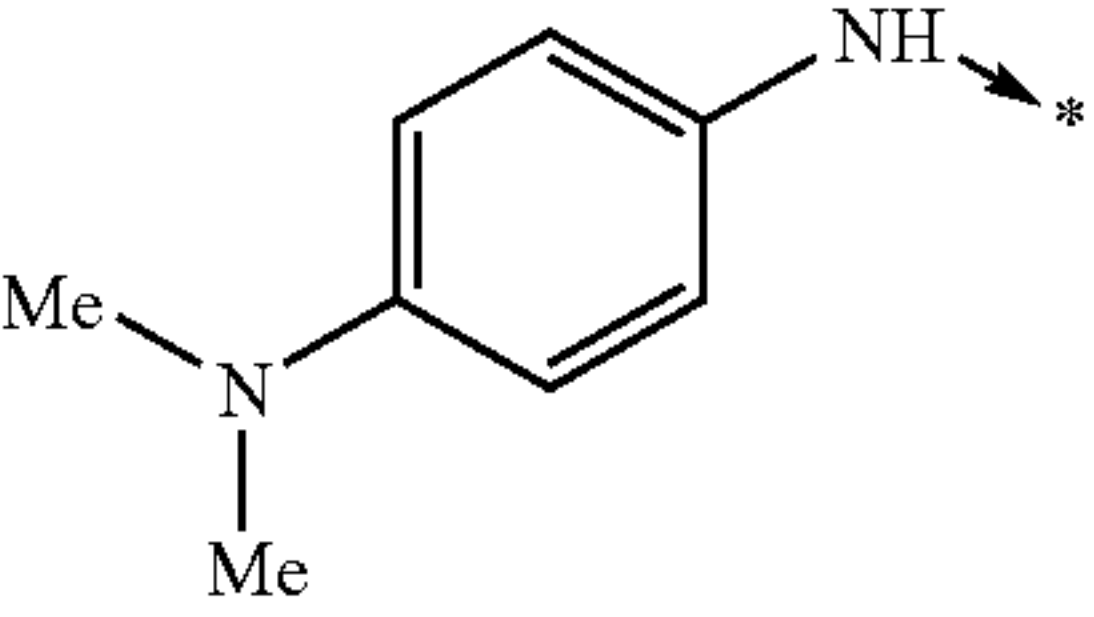
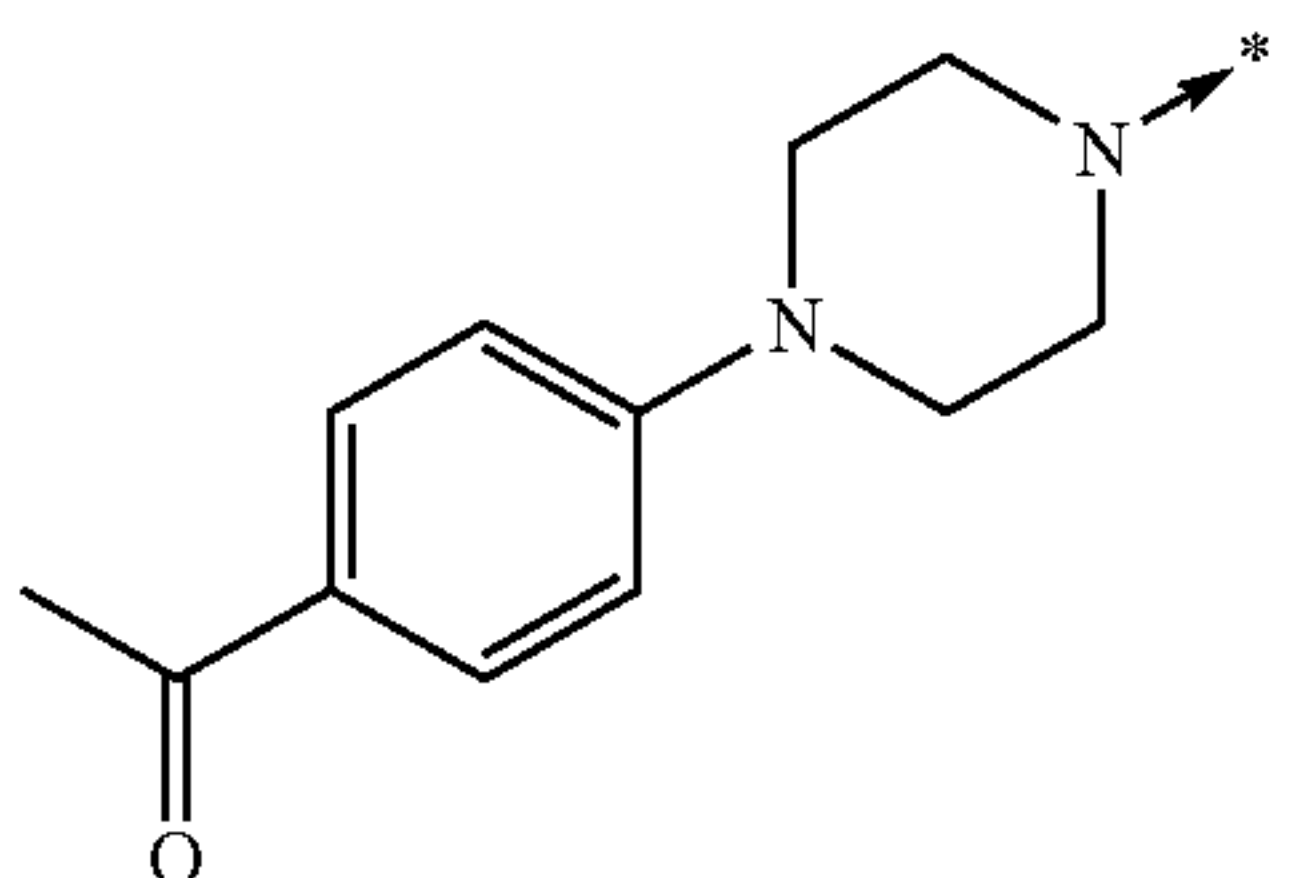
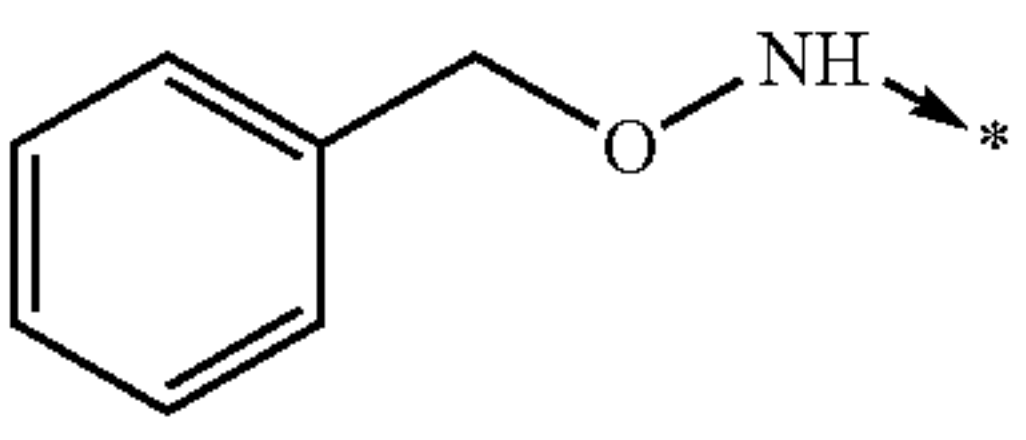
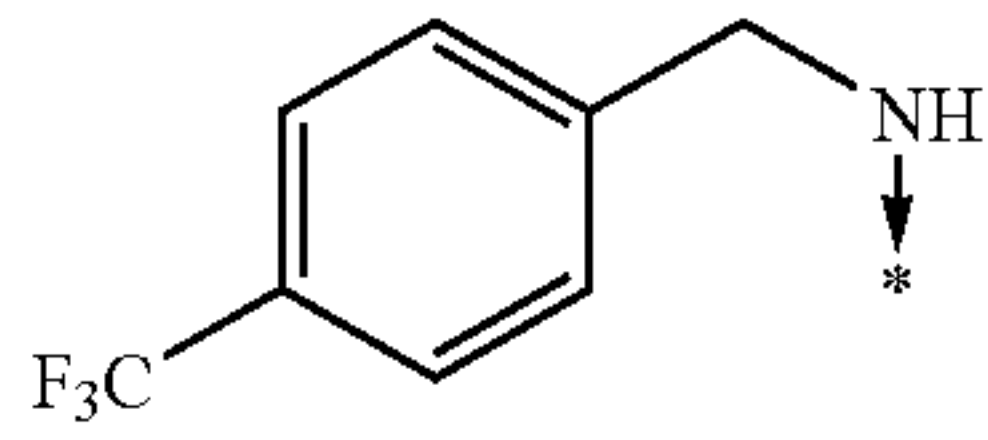
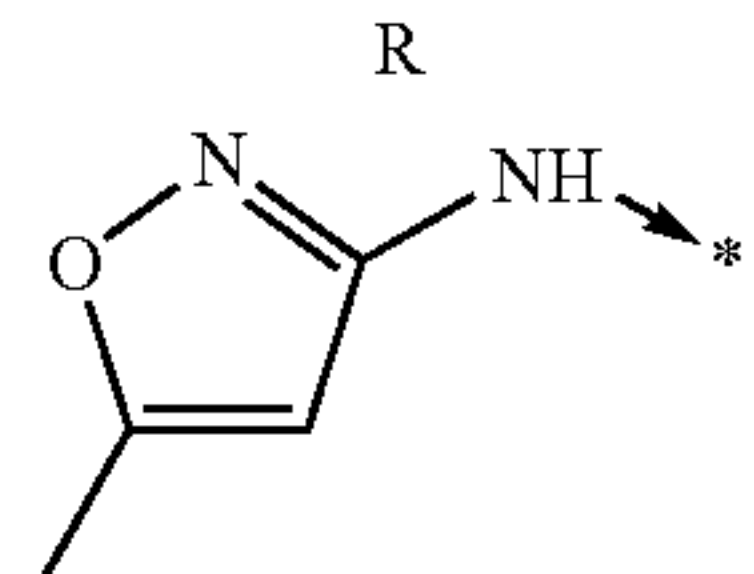
basic structure				
				
R				
				
Example 885	Example 886	Example 887	Example 888	Example 889
100%, 3.653	99%, 3.739	87%, 4.210	99%, 4.276	95%, 4.051
609(M + 1)	653(M + 1)	633(M + 1)	667(M + 1)	726(M + 1)
R				
				
Example 890	Example 891	Example 892	Example 893	Example 894
96%, 3.538	94%, 4.170	97%, 4.352	98%, 3.417	98%, 3.524
662(M + 1)	691(M + 1)	633(M + 1)	710(M + 1)	712(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 15-3

basic structure		
		
R		
		
Example 895 99%, 3.986 623(M + 1)	Example 896 90%, 3.998 777(M + 1)	Example 897 96%, 4.339 767(M + 1)
R		
		
Example 898 96%, 4.579 733(M + 1)	Example 899 98%, 3.903 748(M + 1)	Example 900 96%, 3.492 698(M + 1)
R		
		
Example 901 98%, 3.887 738(M + 1)	Example 902 92%, 4.220 657(M + 1)	Example 903 98%, 4.340 709(M + 1)
R		
		
Example 904 98%, 4.054 632(M + 1)		

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 15-4

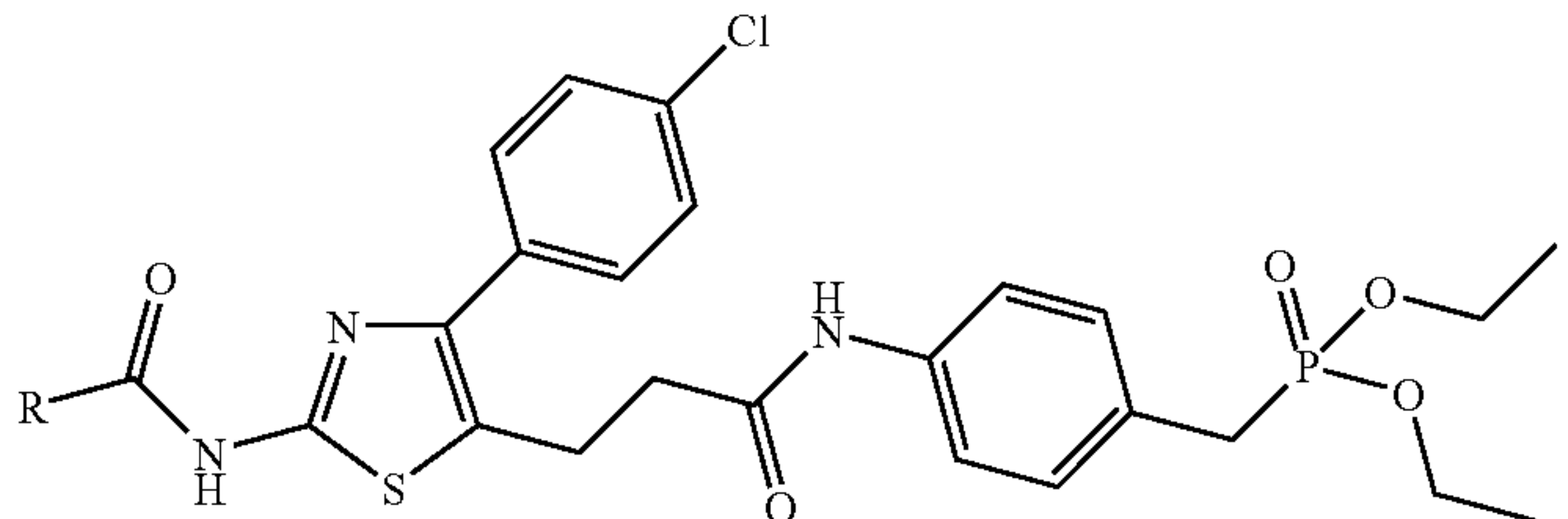
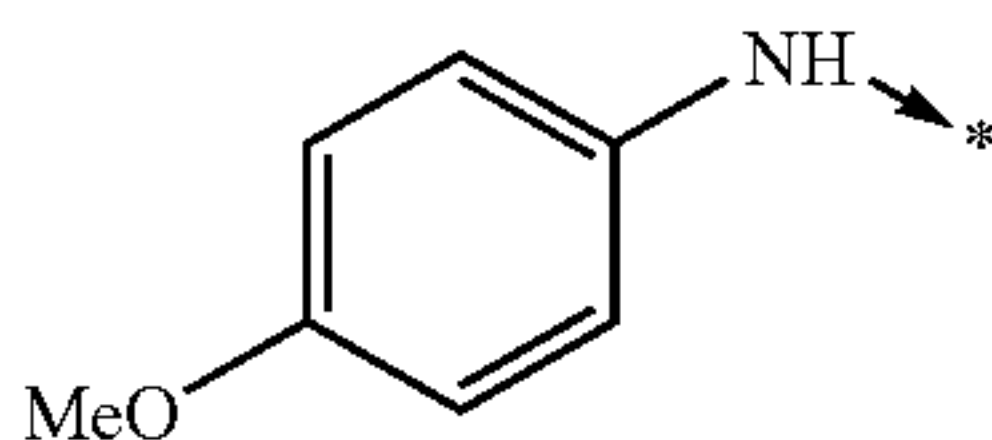
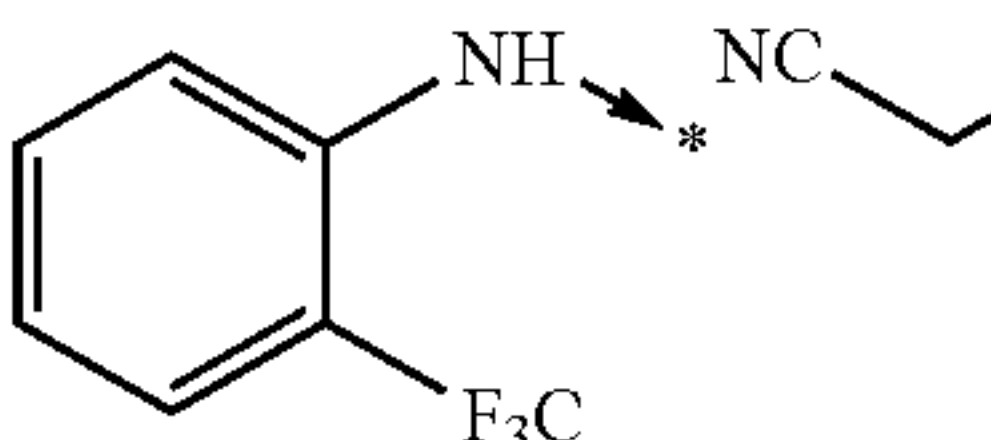
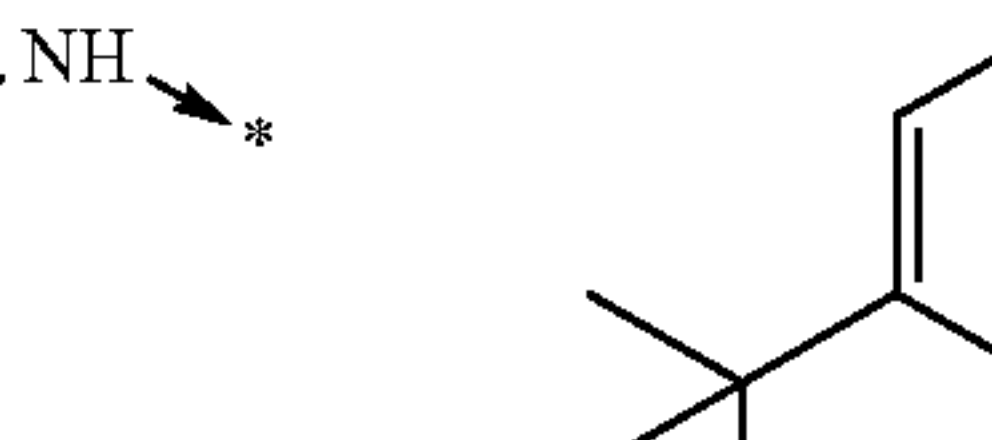
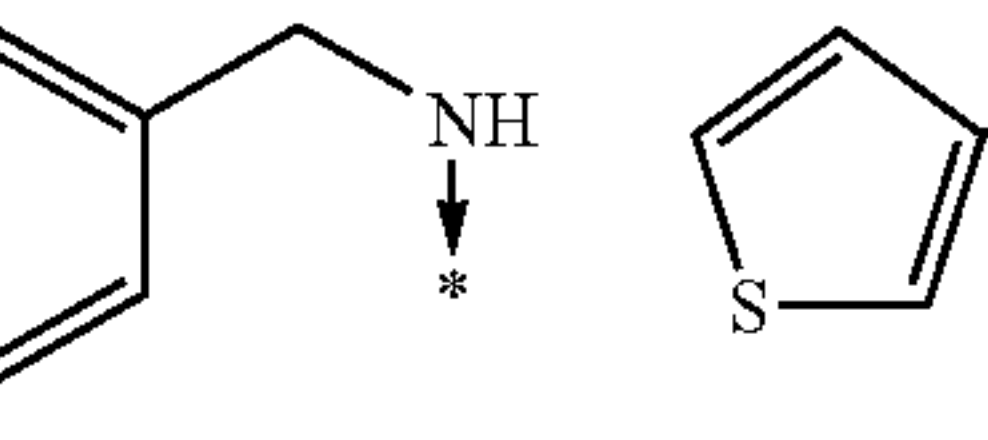

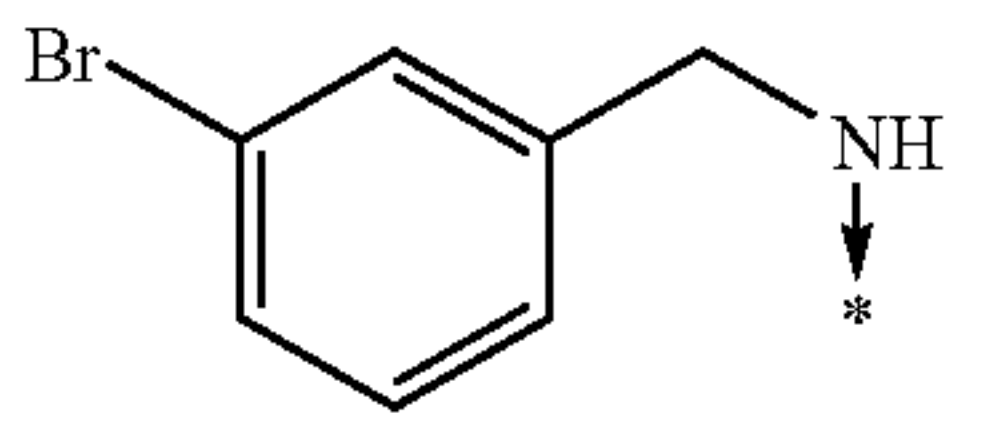
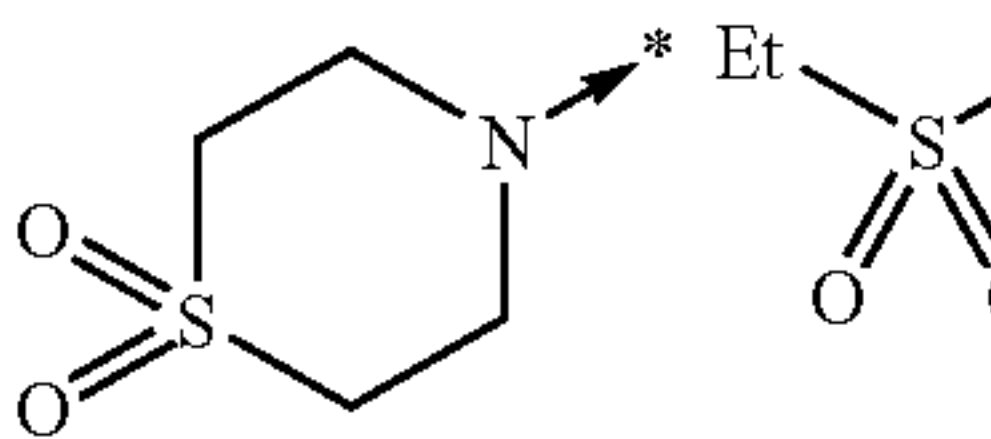
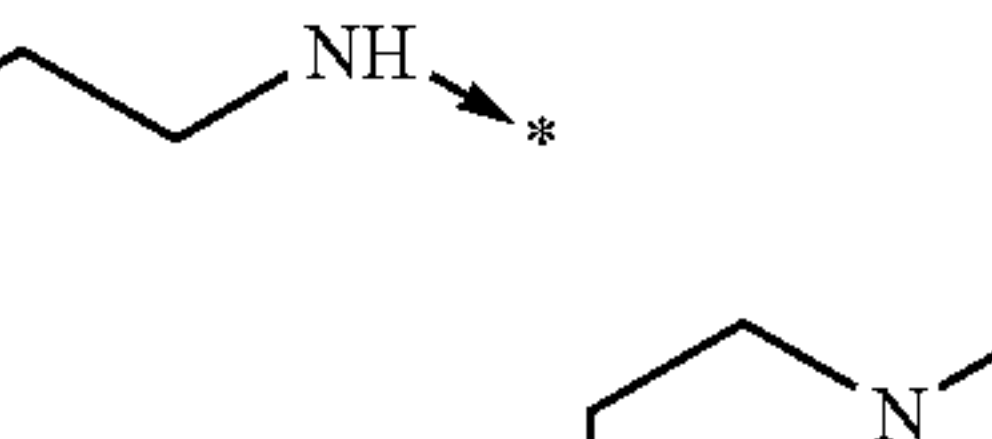
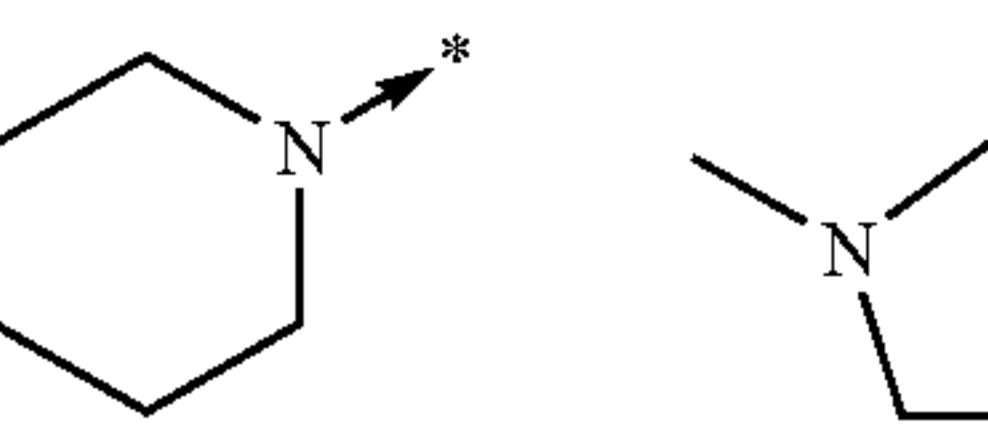
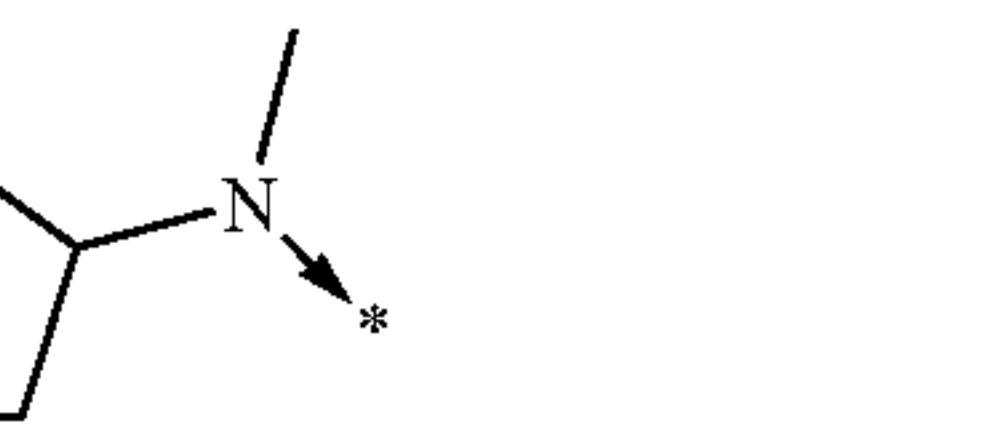
basic structure			
R			
Example 905	Example 906	Example 907	Example 908
99%, 3.996	99%, 4.343	99%, 3.230	100%, 3.230
633(M + 1)	689(M + 1)	642(M + 1)	659(M + 1)
R			
Example 909	Example 910	Example 911	Example 912
86%, 4.362	97%, 4.407	99%, 4.150	97%, 4.133
709(M + 1)	681(M + 1)	714(M + 1)	709(M + 1)
R			
Example 913	Example 914		
100%, 3.676	99%, 3.732		
604(M + 1)	734(M + 1)		

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 16-1

basic structure				
				
R				
				
Example 915 96%, 4.152 657(M + 1)	Example 916 100%, 4.317 657(M + 1)	Example 917 100%, 3.796 590(M + 1)	Example 918 98%, 4.609 697(M + 1)	Example 919 100%, 4.056 647(M + 1)
R				
				
Example 920 100%, 4.314 720(M + 1)	Example 921 100%, 3.696 669(M + 1)	Example 922 100%, 3.641 671(M + 1)	Example 923 100%, 3.284 702(M + 1)	Example 924 100%, 3.243 648(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 16-2

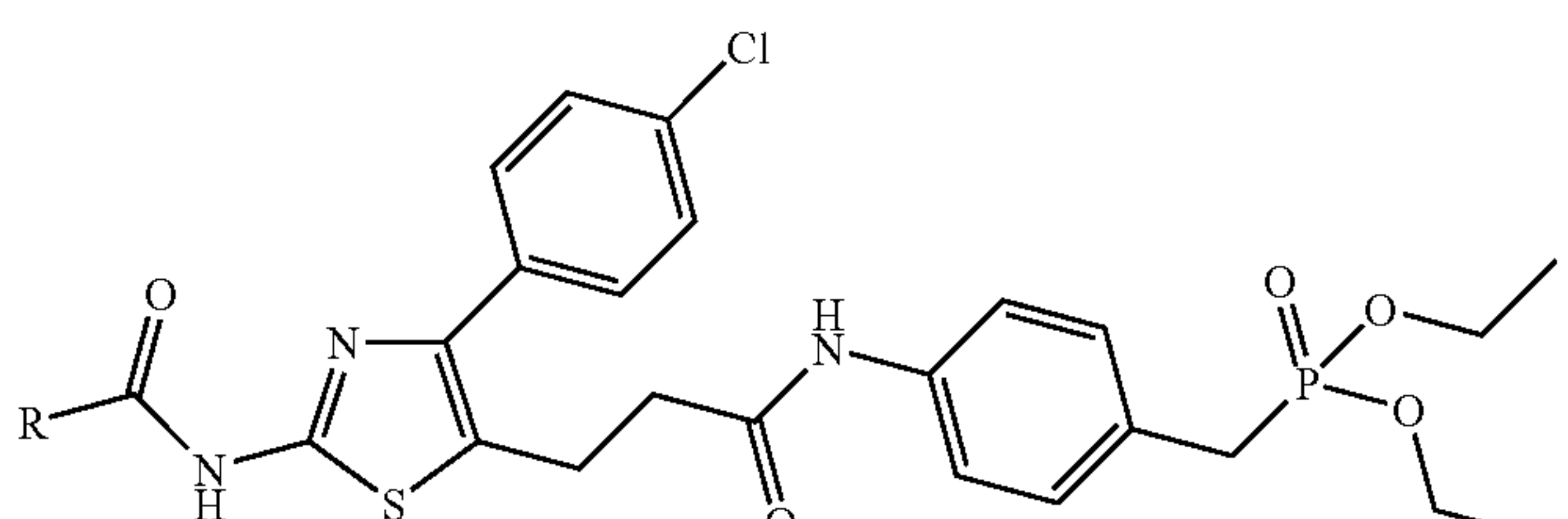
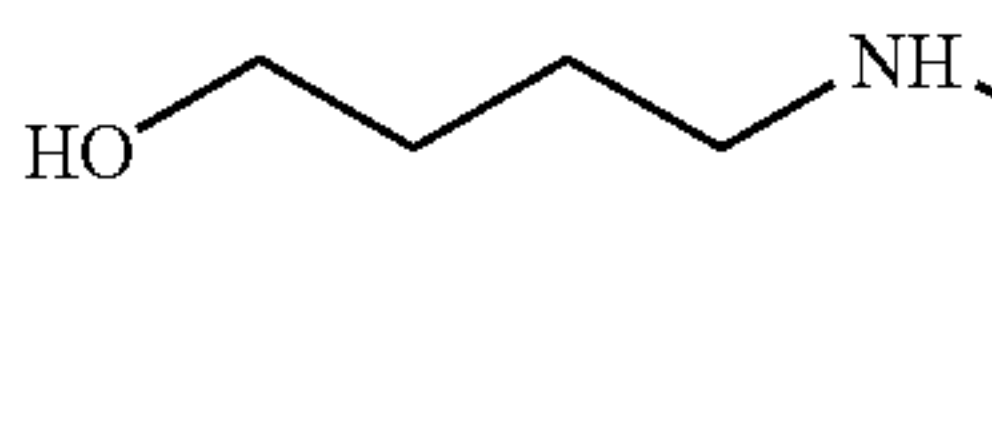
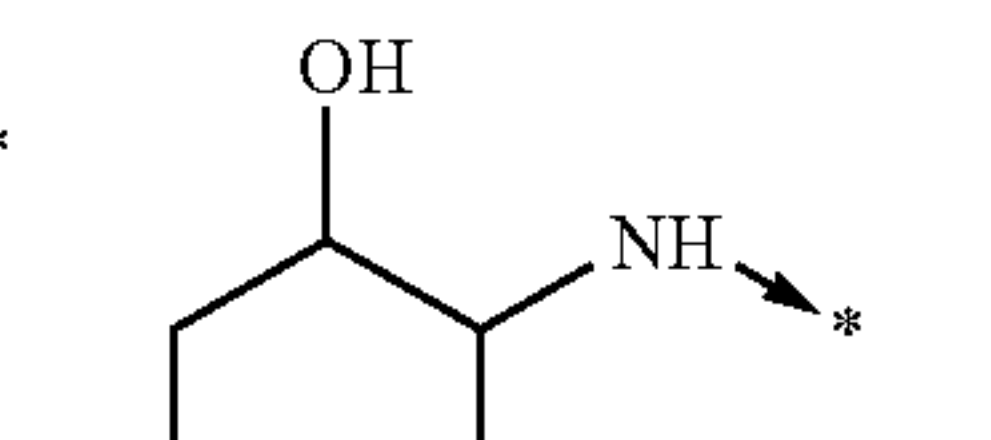
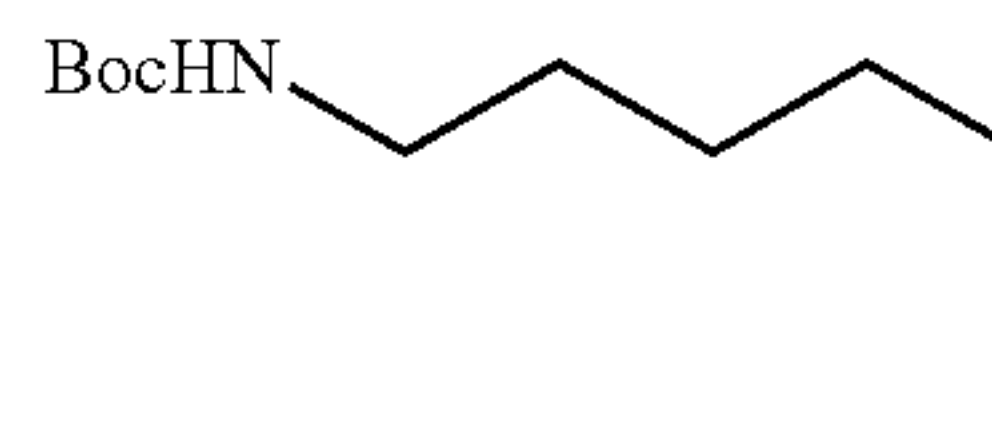
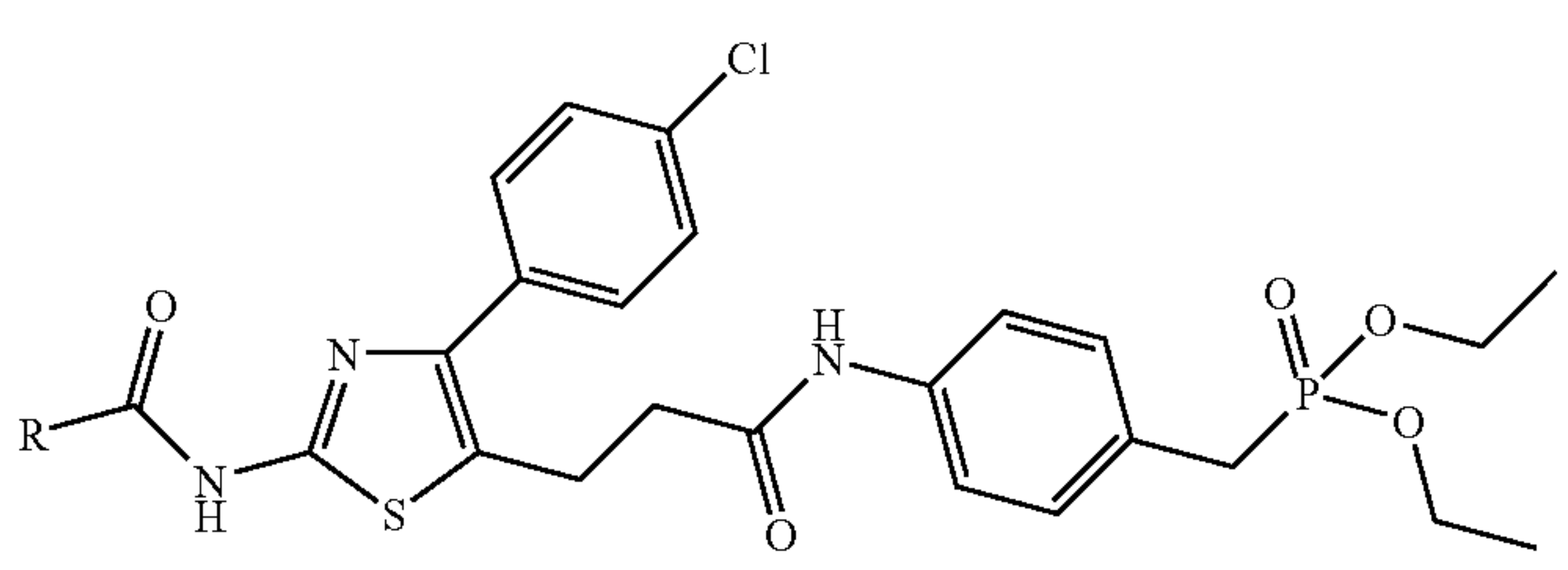
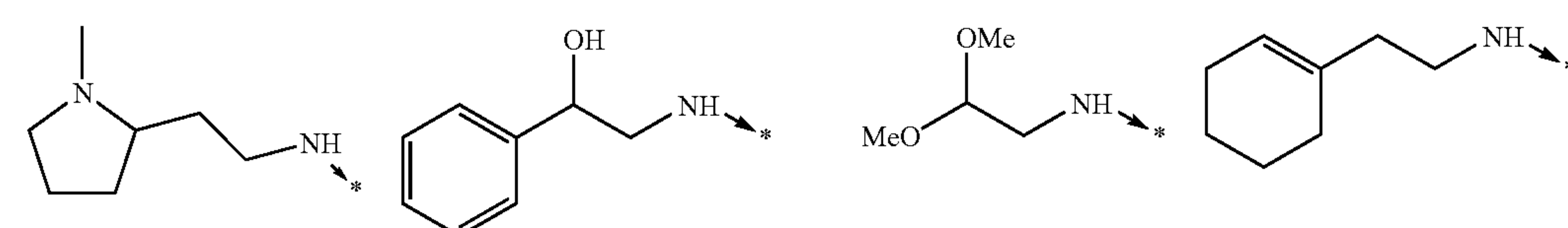
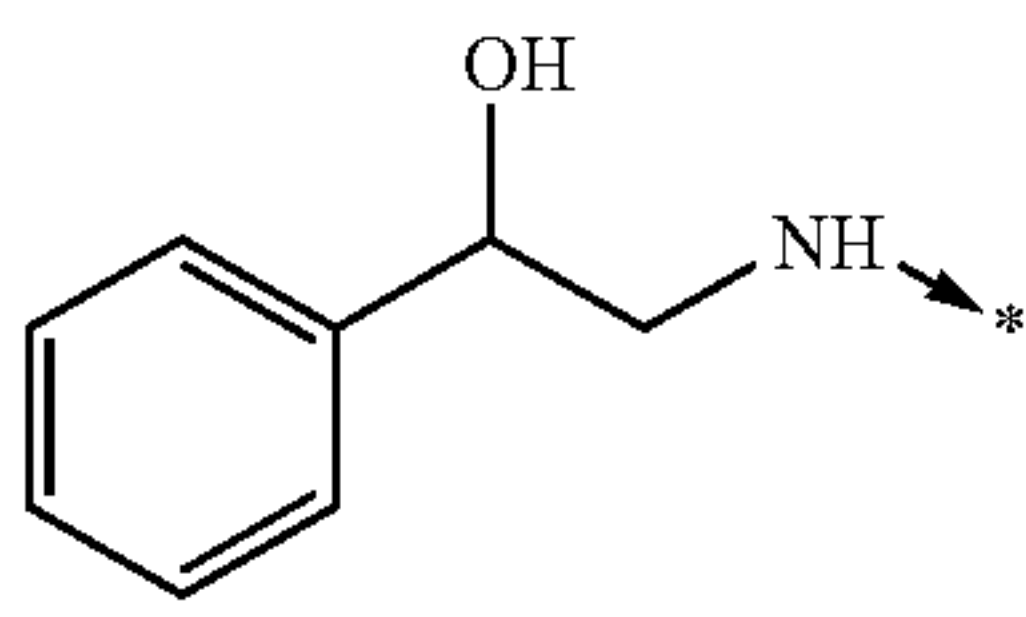
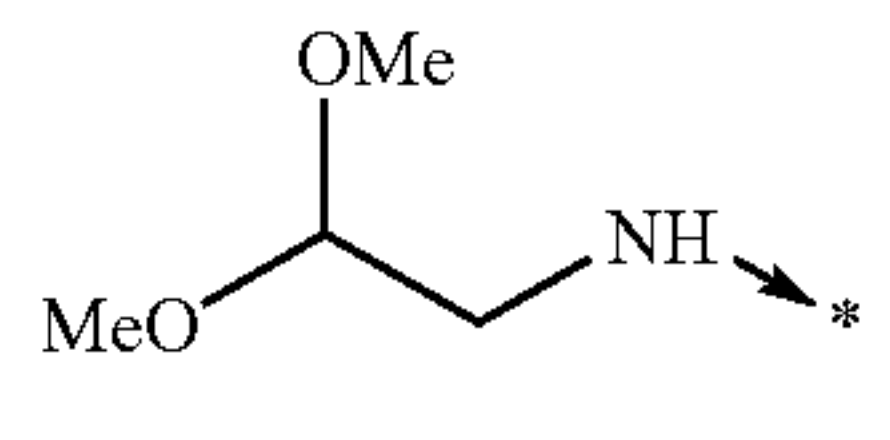
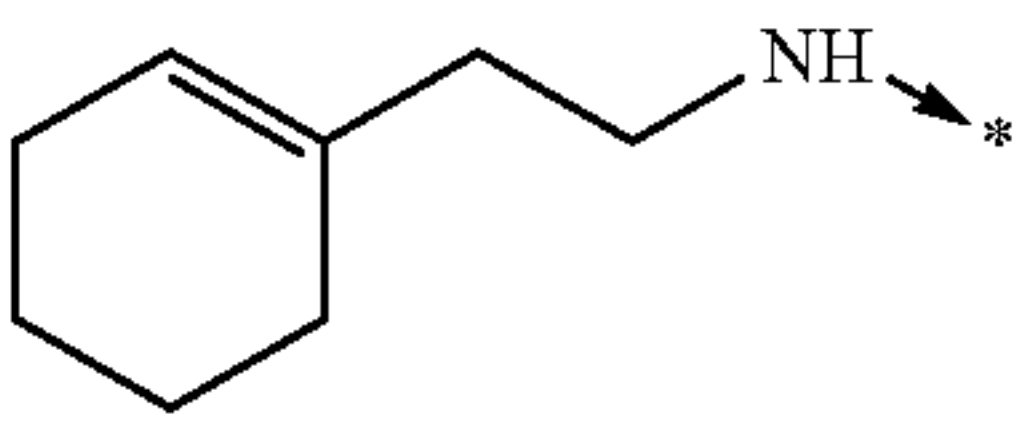
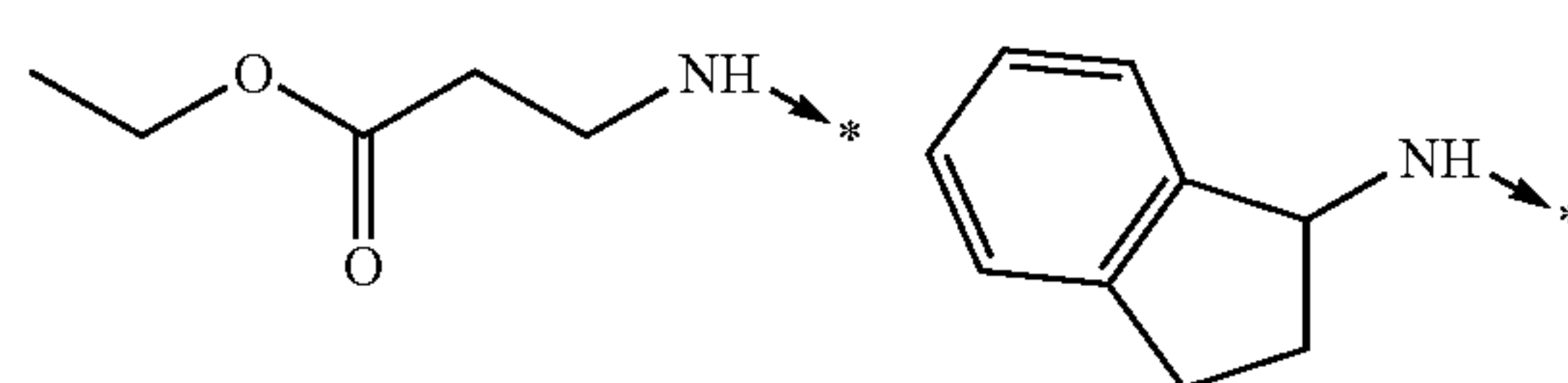
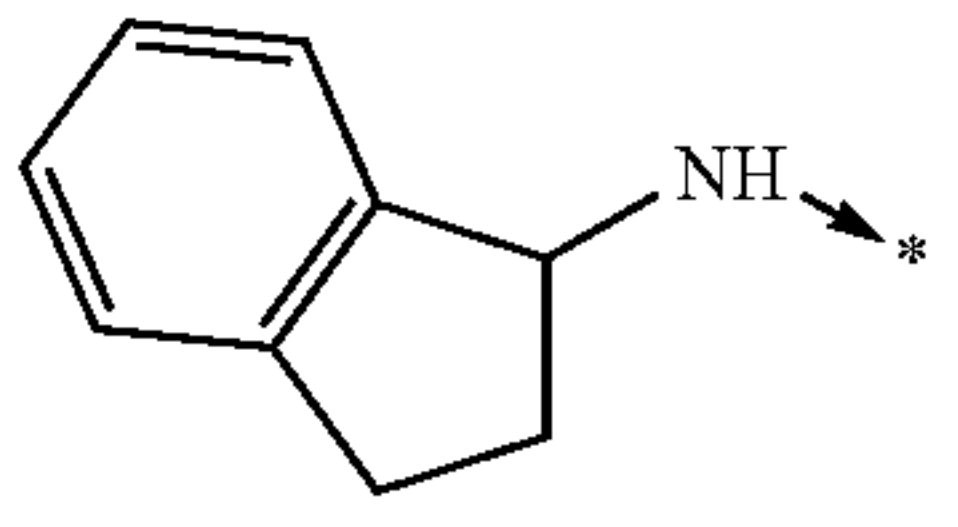
basic structure			
			
R			
			
Example 925 99%, 3.488 623(M + 1)	Example 926 95%, 3.762 649(M + 1)	Example 927 80%, 4.136 736(M + 1)	Example 928 99%, 3.227 664(M + 1)
R			

TABLE 16-2-continued

basic structure			
			
			
Example 929 100%, 3.245 662(M + 1)	Example 930 99%, 3.856 671(M + 1)	Example 931 89%, 3.735 639(M + 1)	Example 932 96%, 4.436 659(M + 1)

R	
	
Example 933 99%, 3.866 651(M + 1)	Example 934 99%, 4.300 667(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 16-3

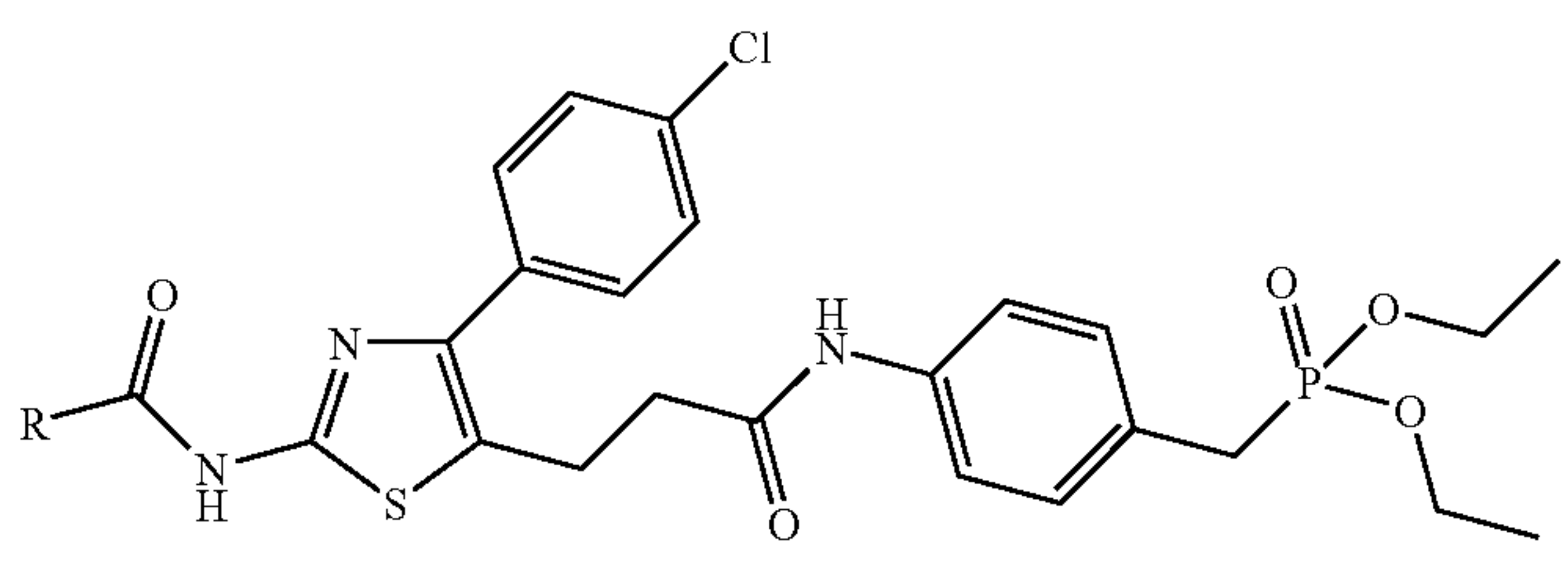
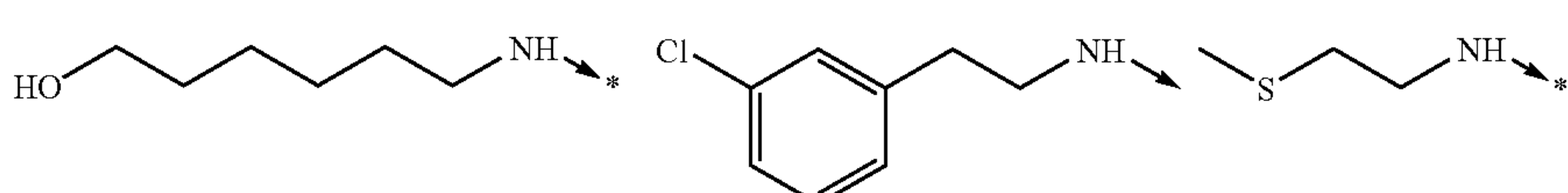
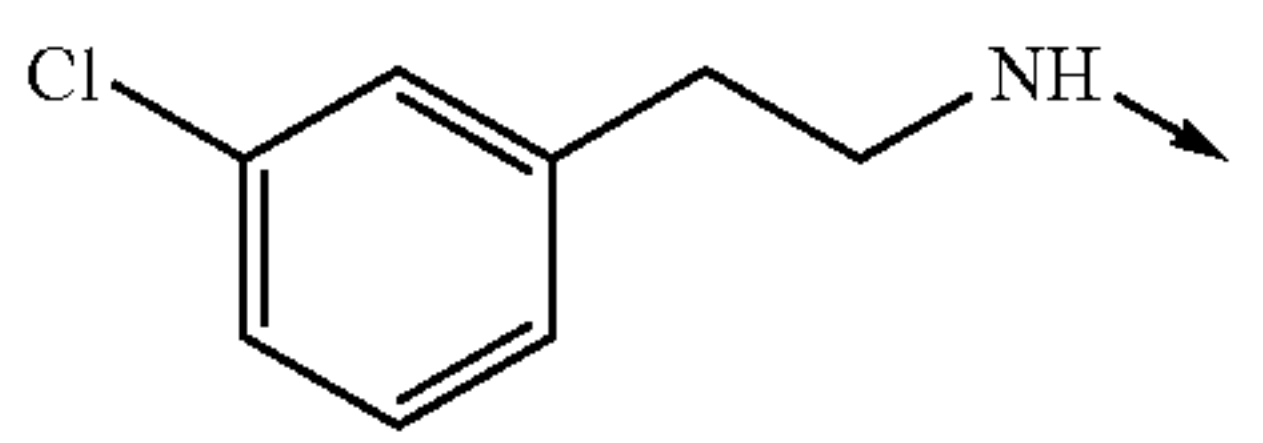
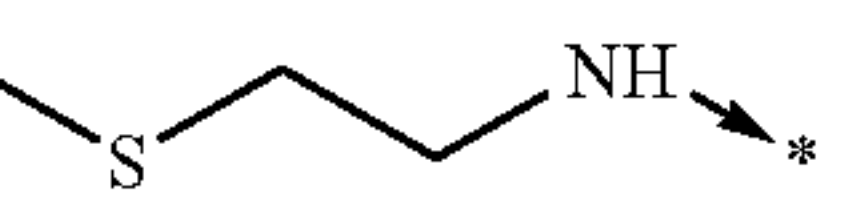
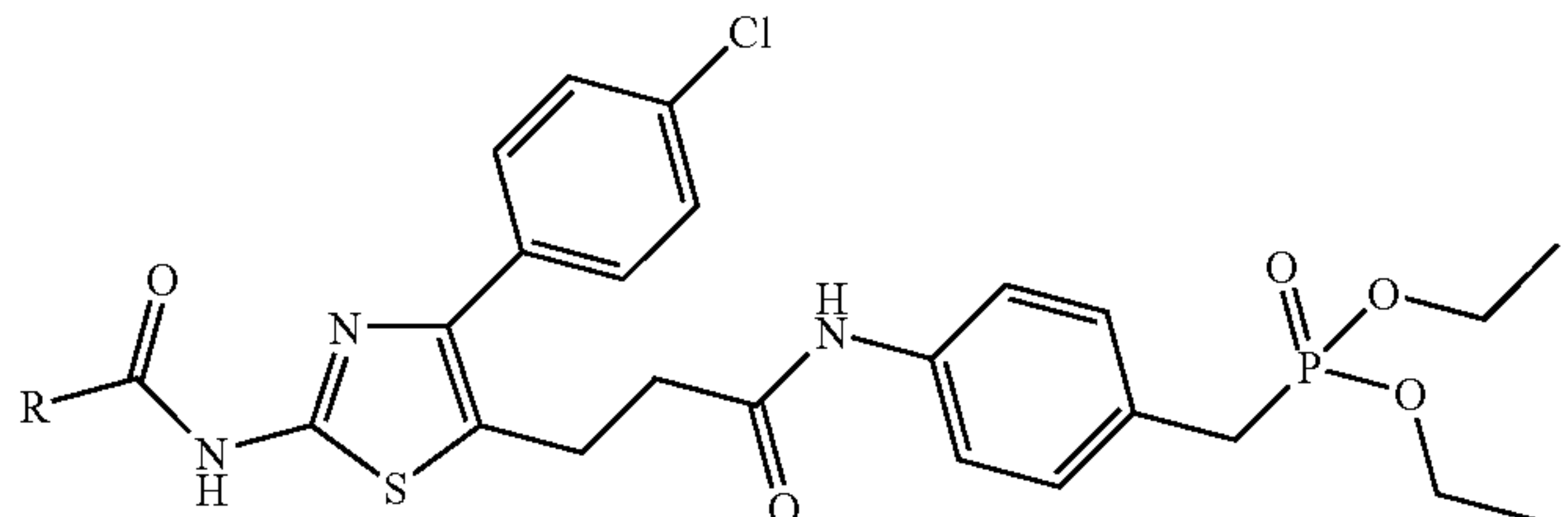
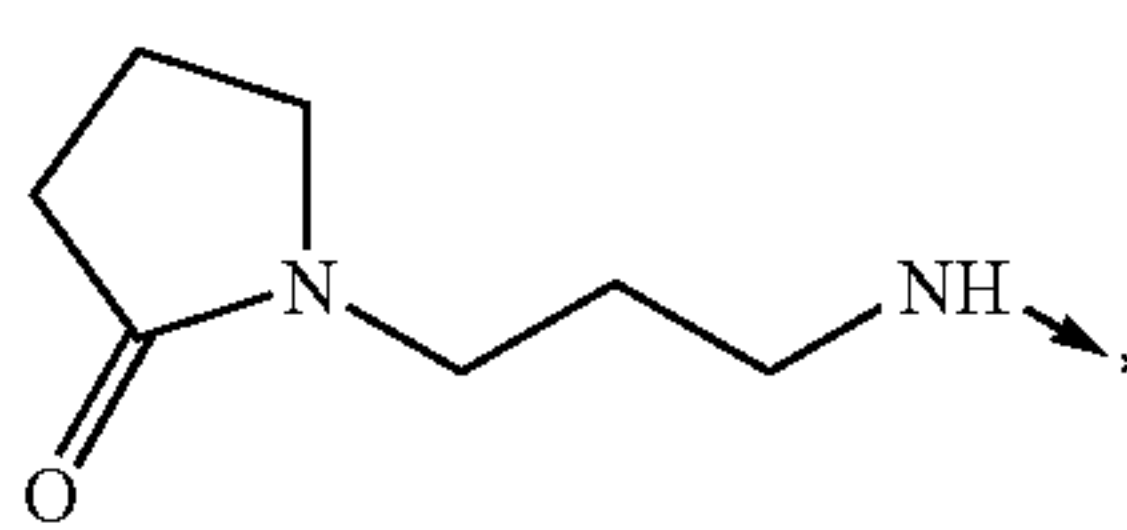
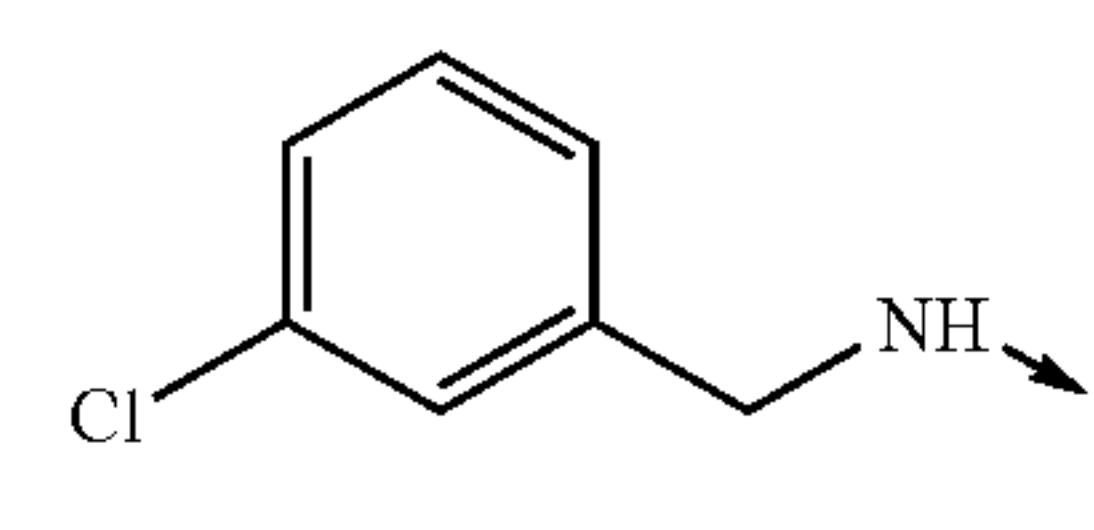
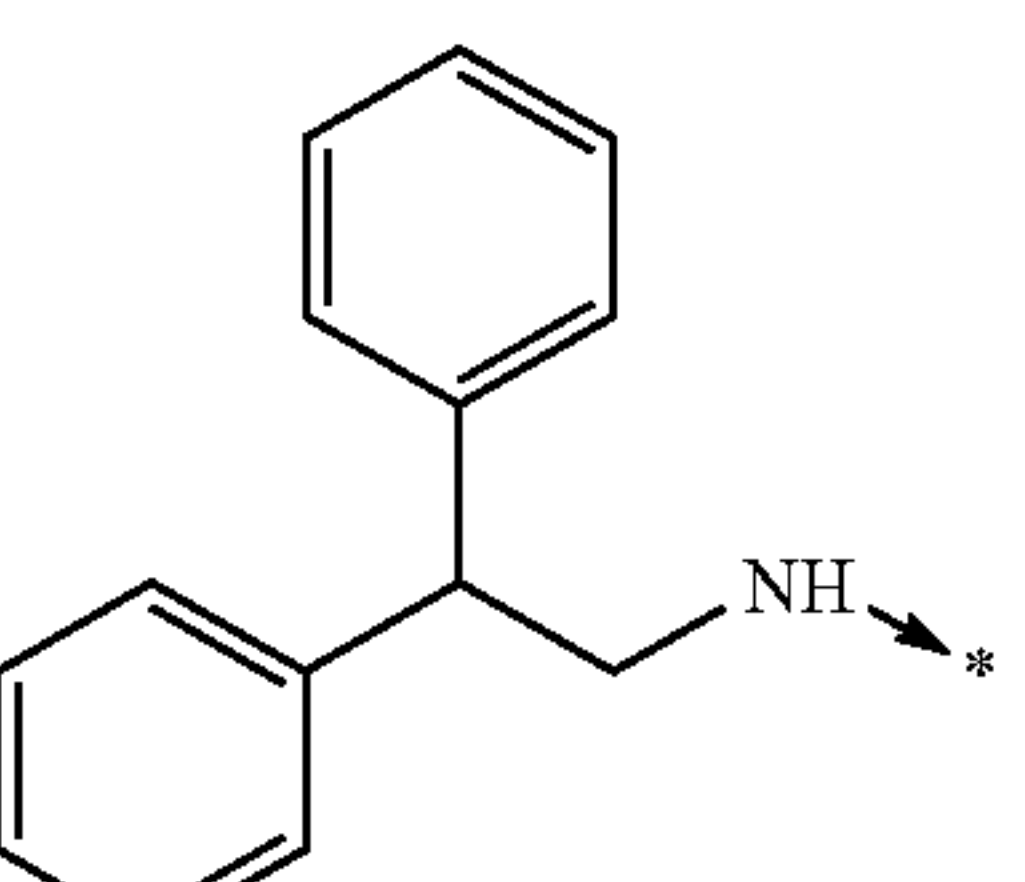
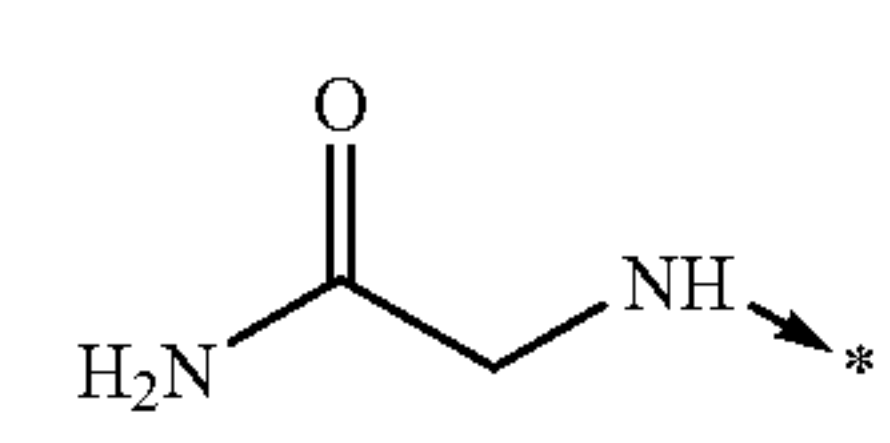
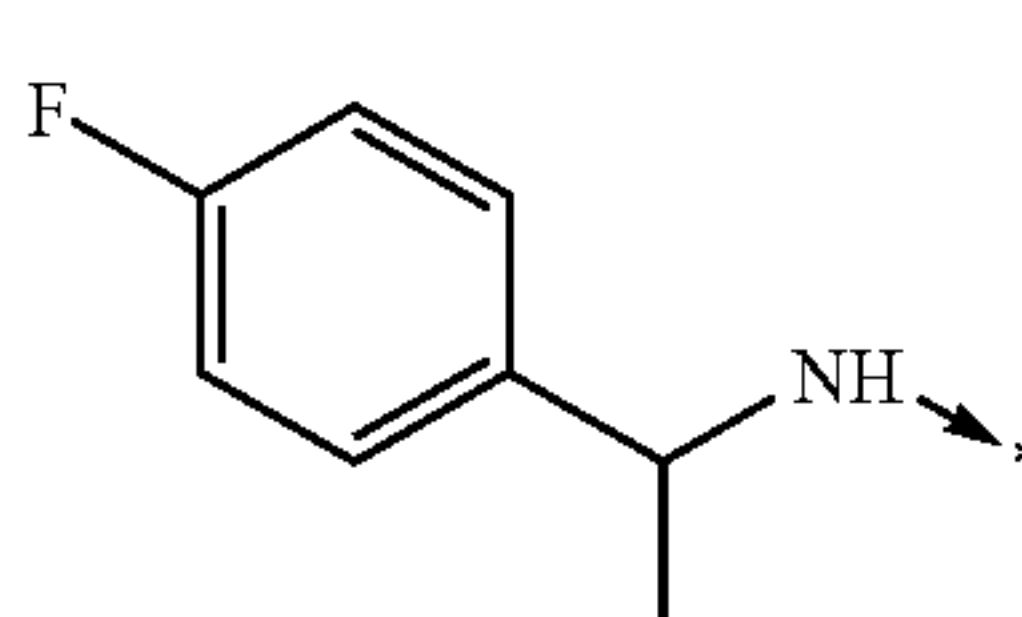
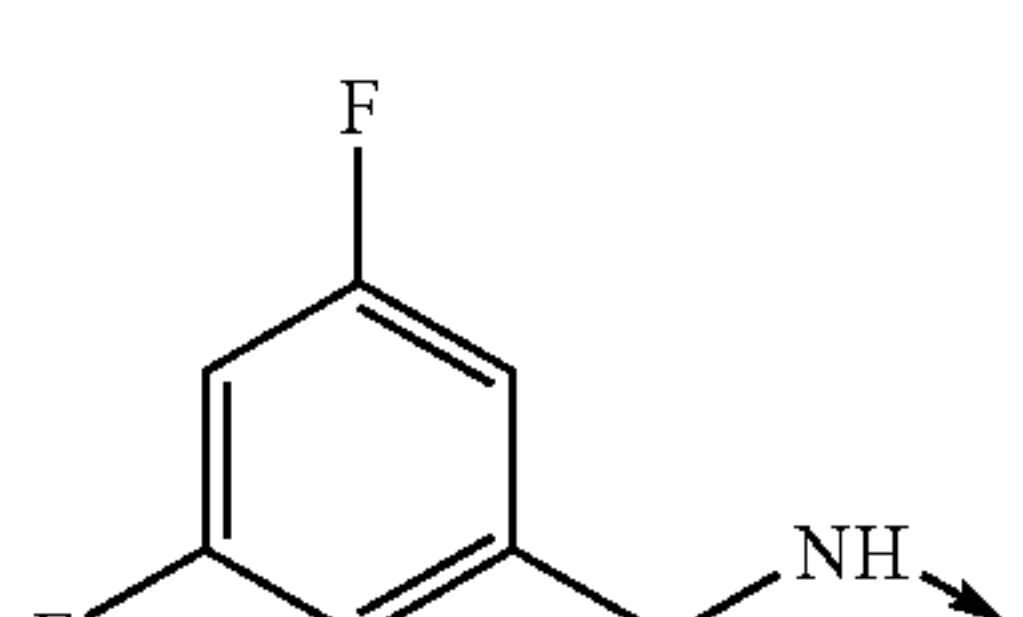
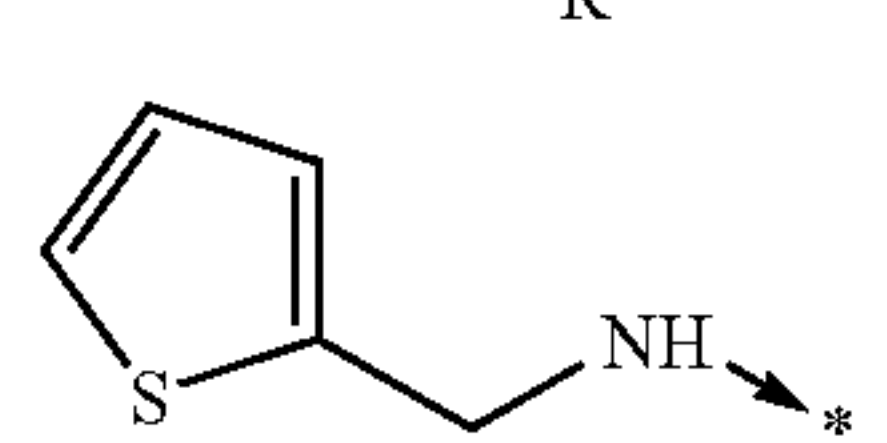
basic structure		
		
R		
		
Example 935 100%, 3.679 651(M + 1)	Example 936 100%, 4.357 689(M + 1)	Example 937 99%, 3.885 625(M + 1)
R		

TABLE 16-3-continued

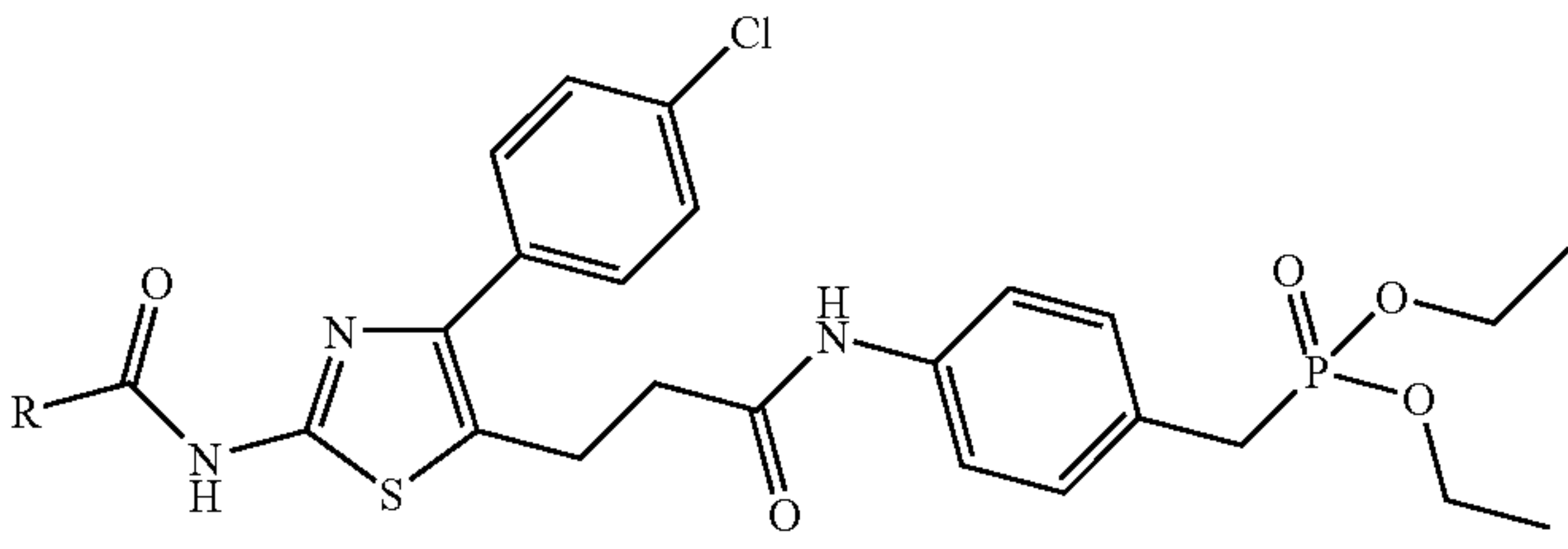
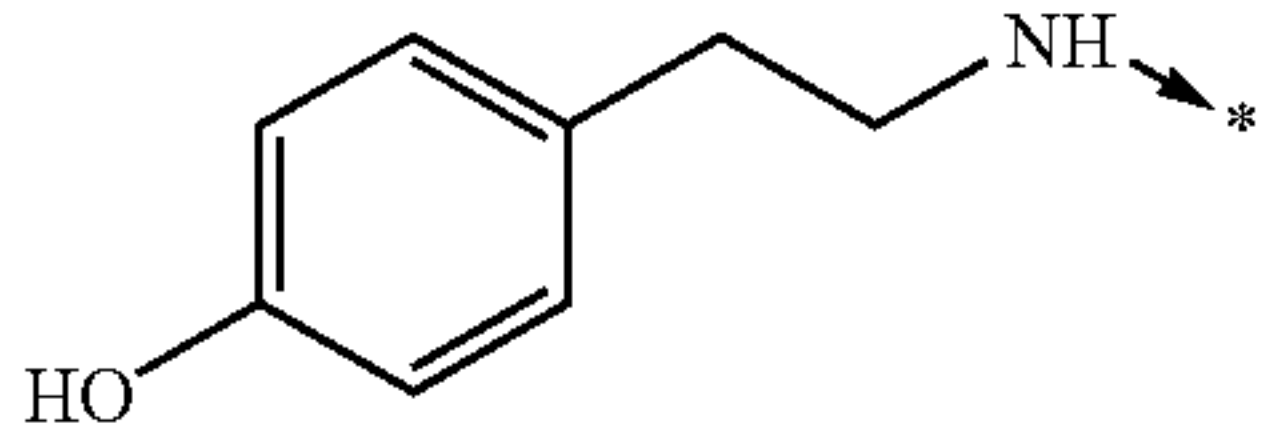
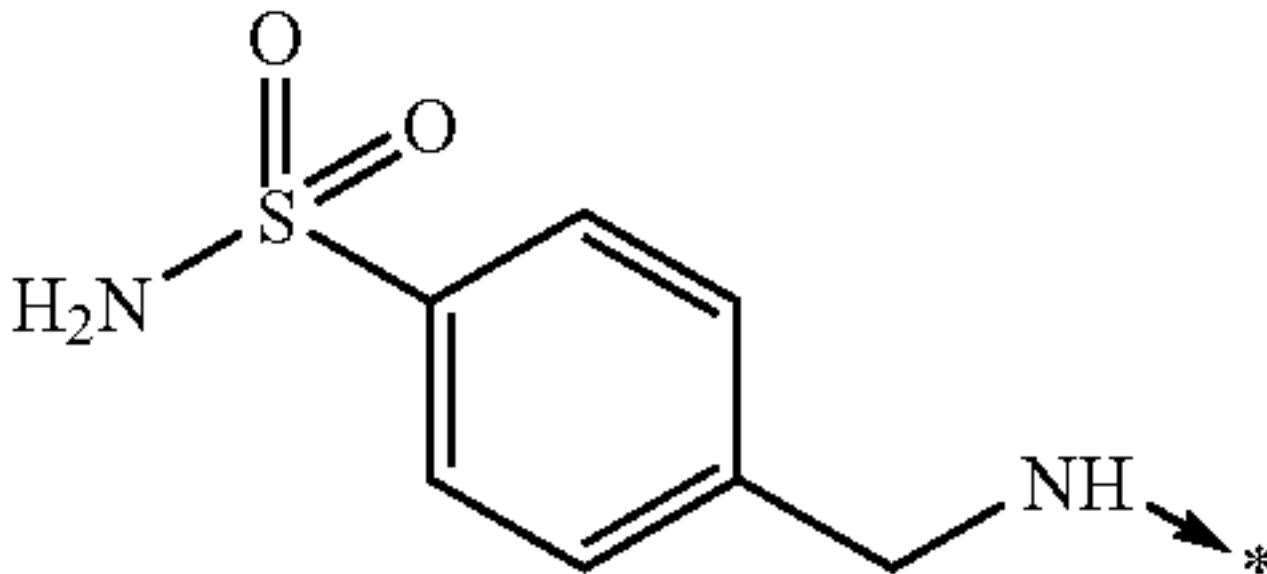
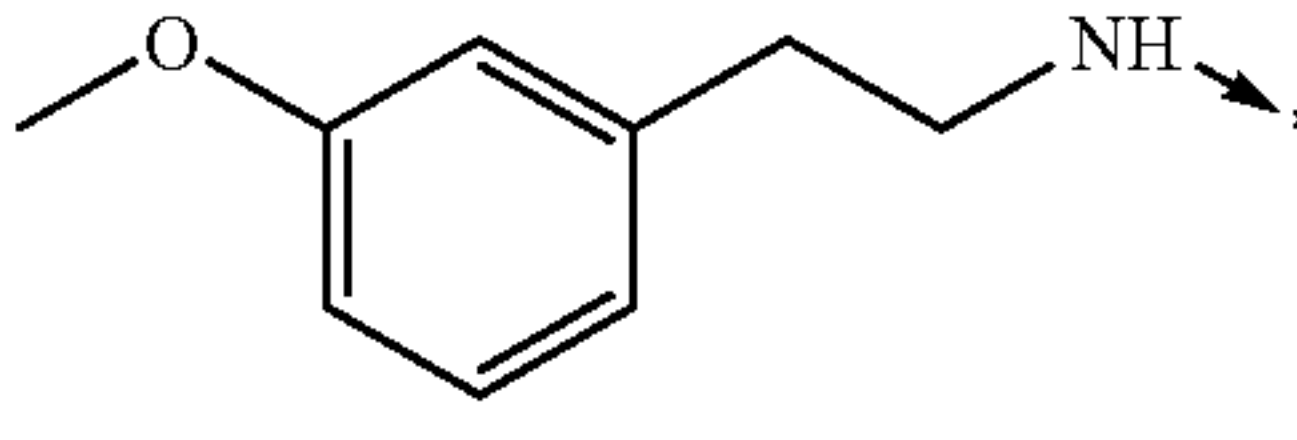
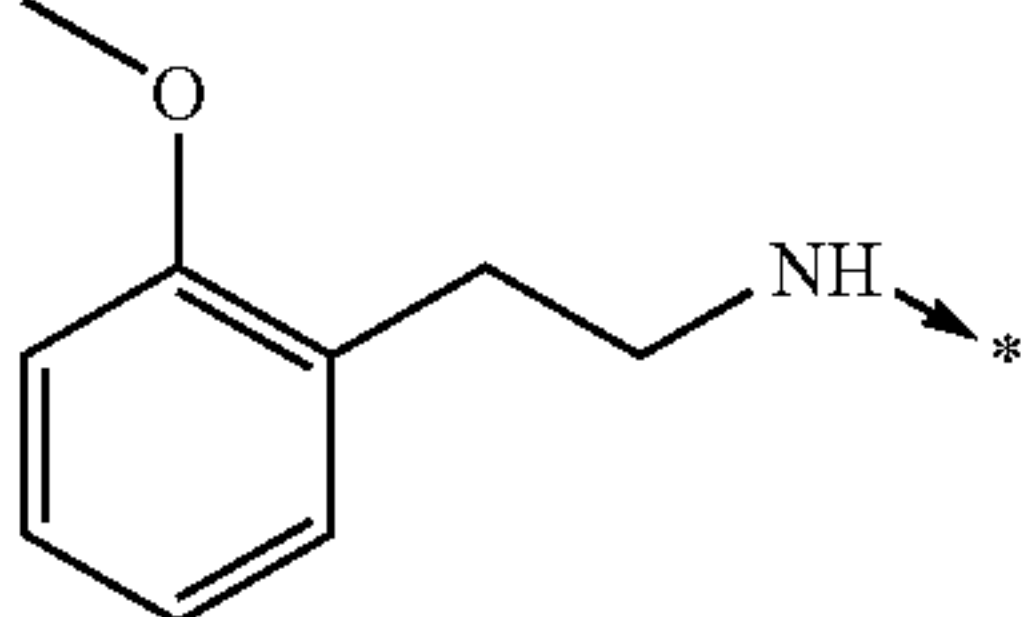
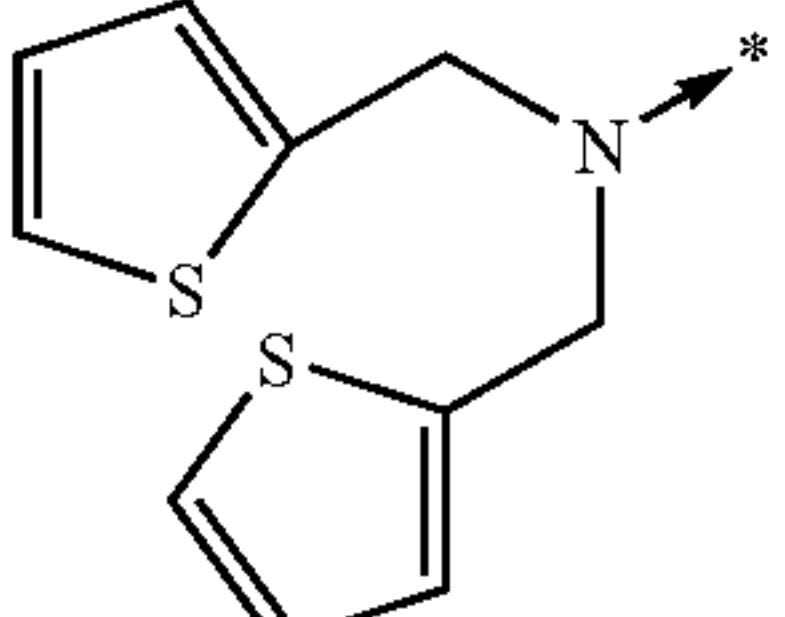
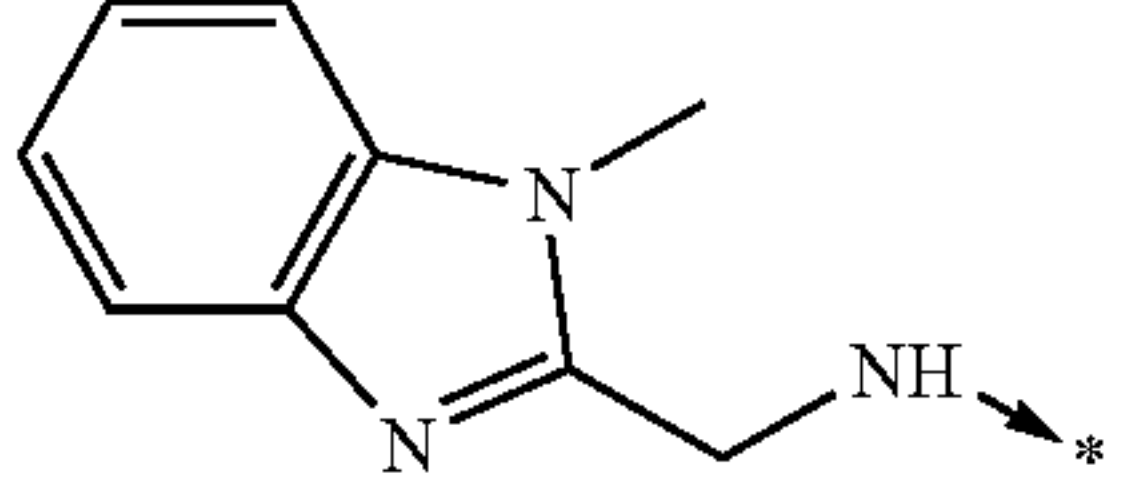
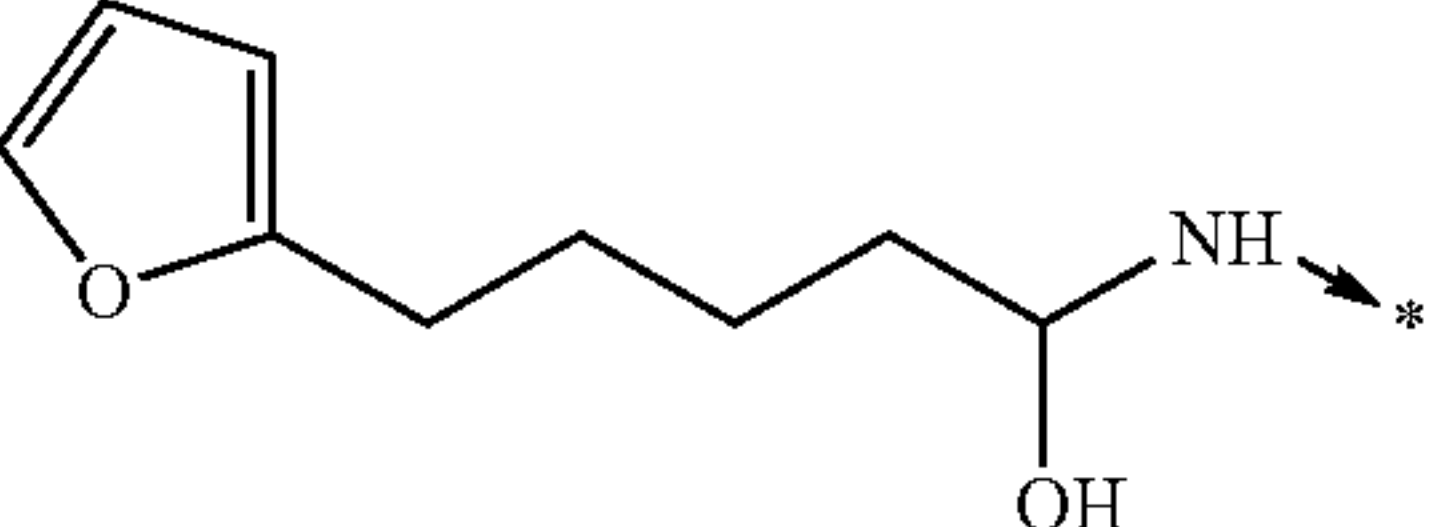
basic structure		
		
		
Example 938	Example 939	Example 940
99%, 3.539	100%, 4.275	99%, 4.518
676(M + 1)	675(M + 1)	731(M + 1)
R		
		
Example 941	Example 942	Example 943
98%, 3.364	99%, 4.241	99%, 4.204
608(M + 1)	673(M + 1)	677(M + 1)
R		
		
Example 944		
99%, 4.057		
647(M + 1)		

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 16-4

basic structure		
		
R		
		
Example 945	Example 946	Example 947
99%, 3.839	100%, 3.717	99%, 4.173
671(M + 1)	720(M + 1)	685(M + 1)
R		
		
Example 948	Example 949	Example 950
99%, 4.281	99%, 4.615	99%, 3.395
685(M + 1)	743(M + 1)	695(M + 1)
R		
		
Example 951		
99%, 4.494		
701(M + 1)		

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

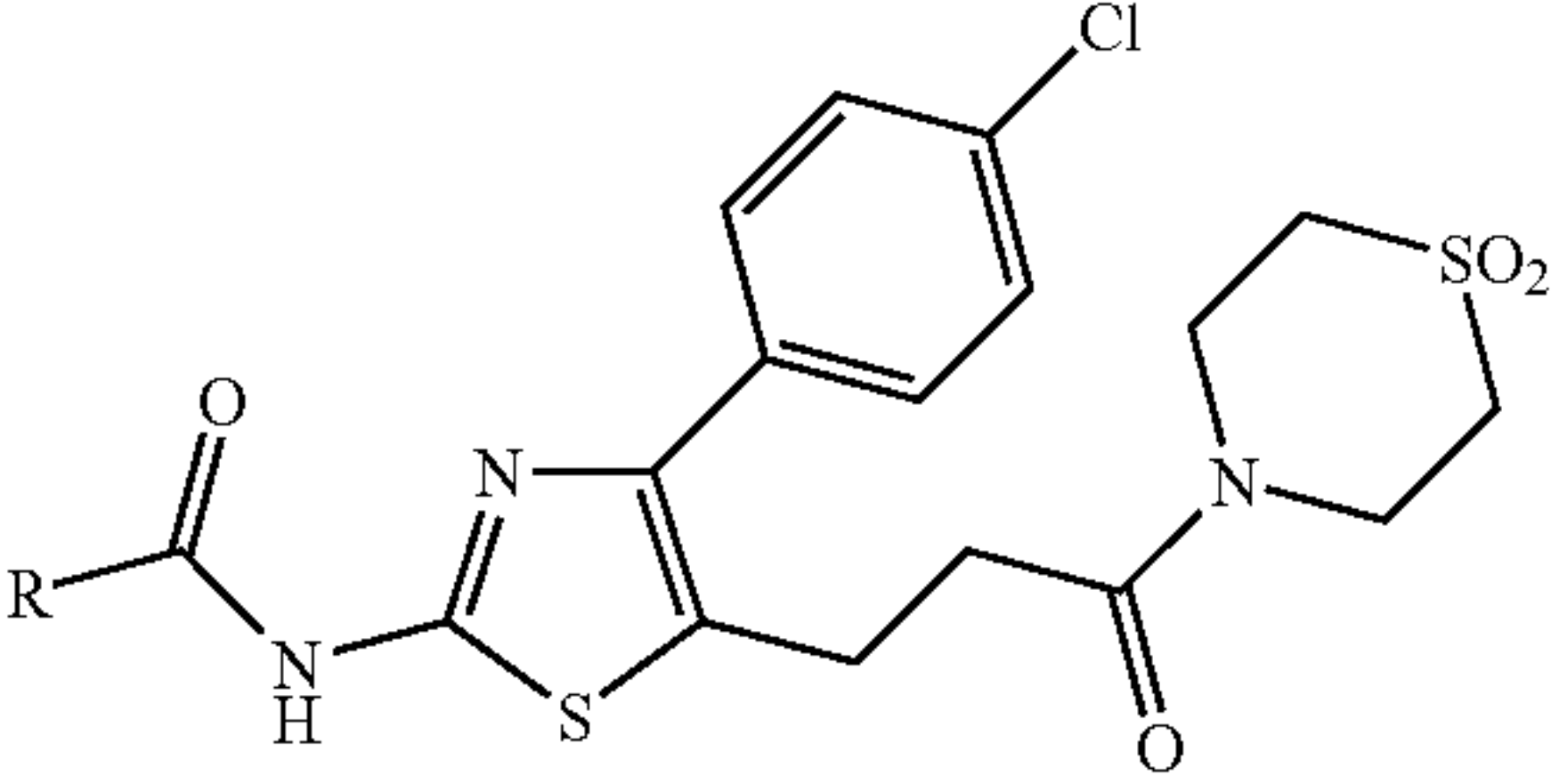
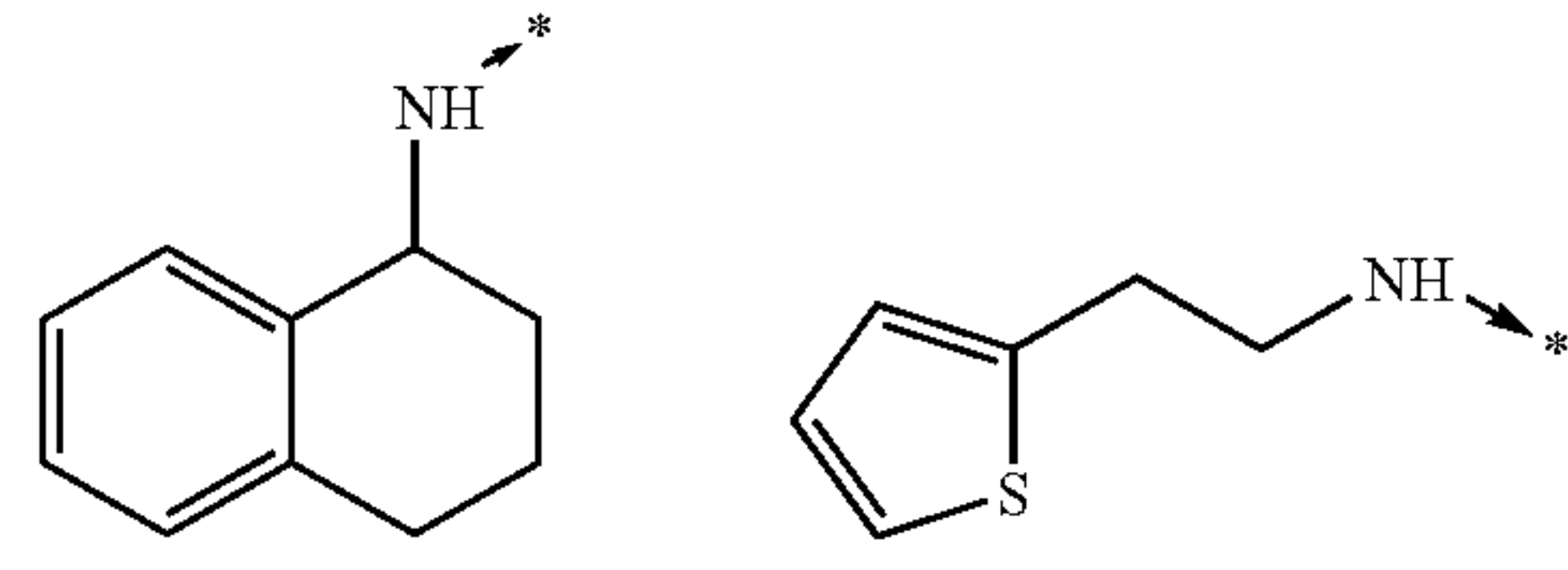
lower line: MS(APCI+, m/e)

261

262

Example 954

TABLE 17

basic structure	
	
R	
	
Example 952	Example 953
99%, 4.005	99%, 3.885
573(M + 1)	553(M + 1)

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

A mixture of diethyl [4-({3-[2-amino-4-(4-chlorophenyl)-1,3-thiazol-5-yl]propanoyl}amino)benzyl]phosphonate (100 mg), cyclohexanecarboxylic acid (38 mg), 1-hydroxy-7-azabenzotriazole (31 mg), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide (76 mg) and N,N-dimethylformamide (0.4 ml) was shaken at room temperature for 8 hrs. The reaction mixture was directly poured into preparative HPLC and purified to give the object compound.

Examples 955–993

In the same manner as in Example 954, the object compounds were obtained.

The structure and purity of the object compounds of Examples 954–993 were confirmed by LC-MS, HPLC. The yield, structure, purity and mass spectrum data of the object compounds are shown in [Table 18-1]–[Table 18-2] and [Table 19-1]–[Table 19-2].

TABLE 18-1

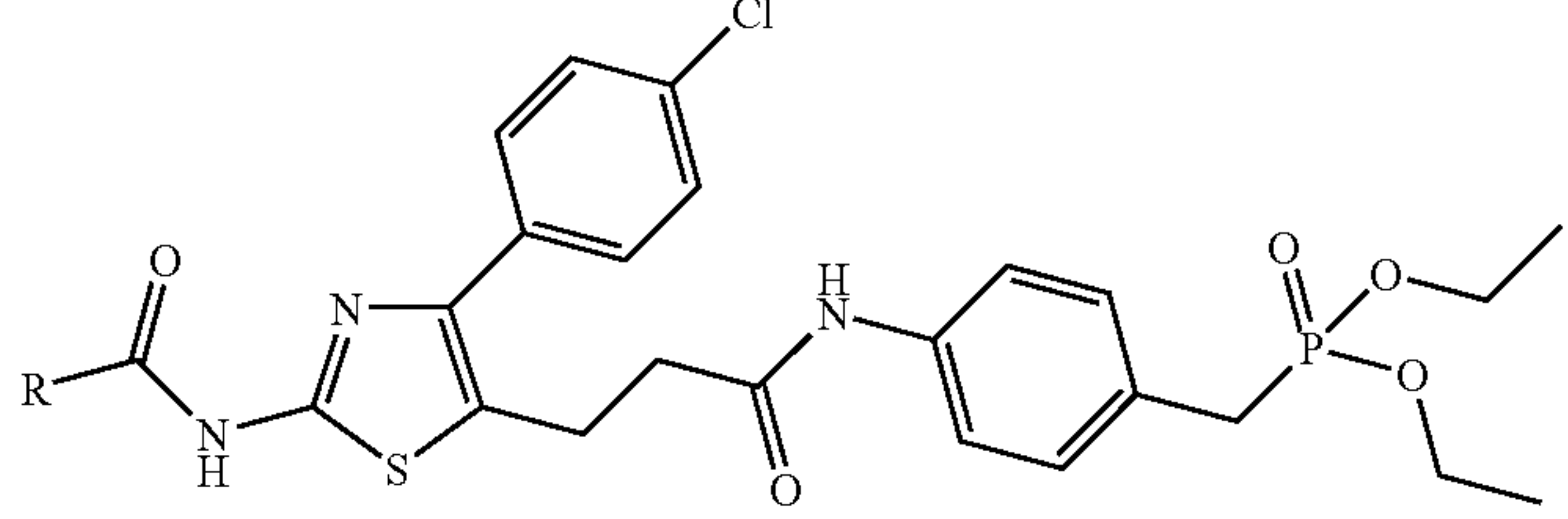
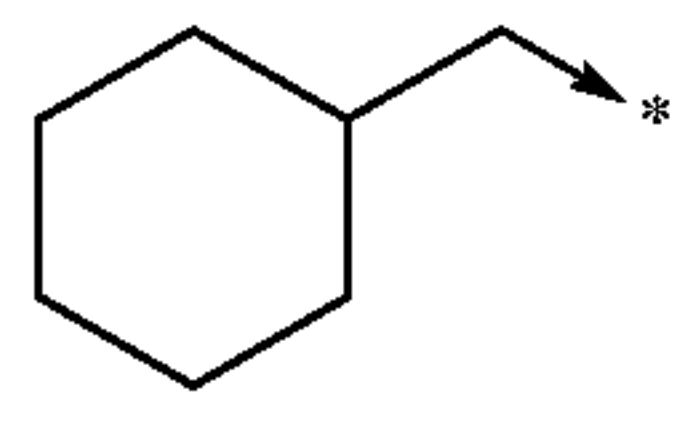
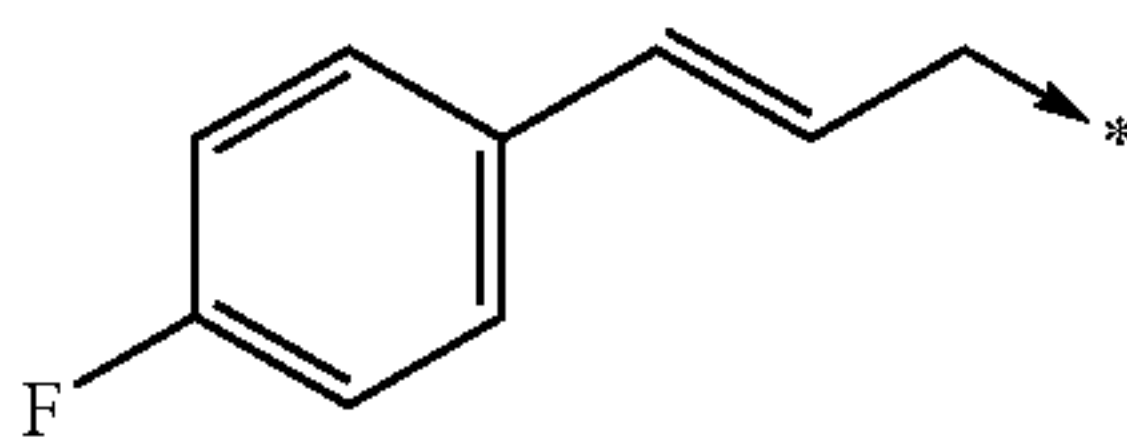
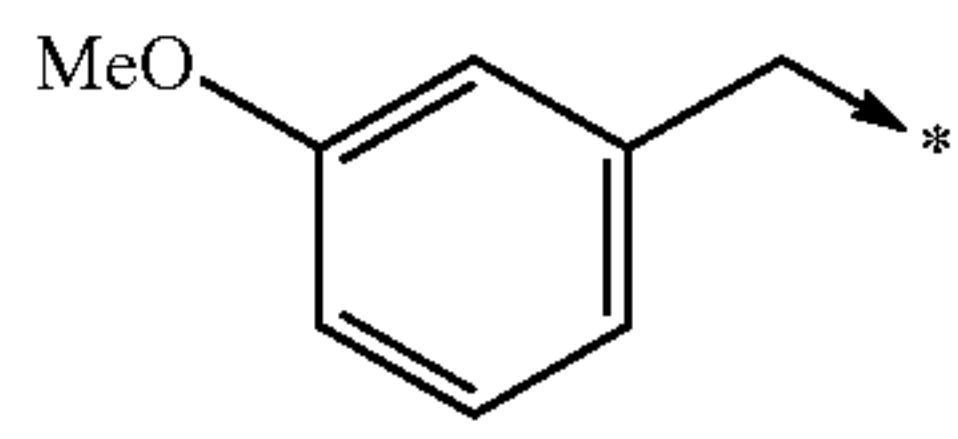
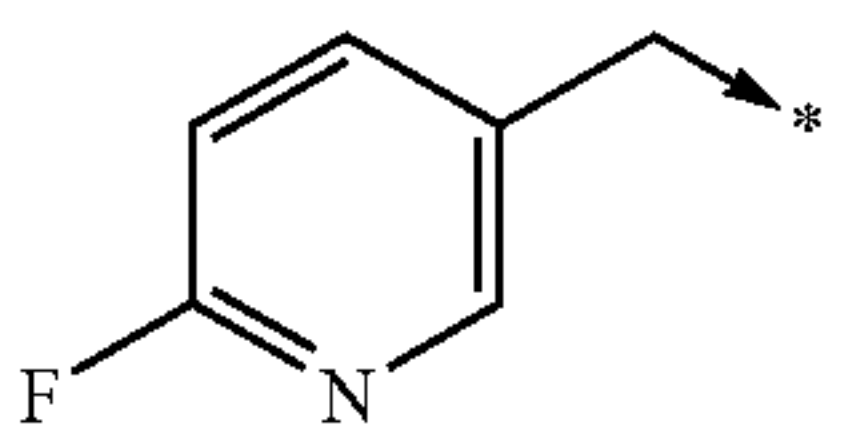
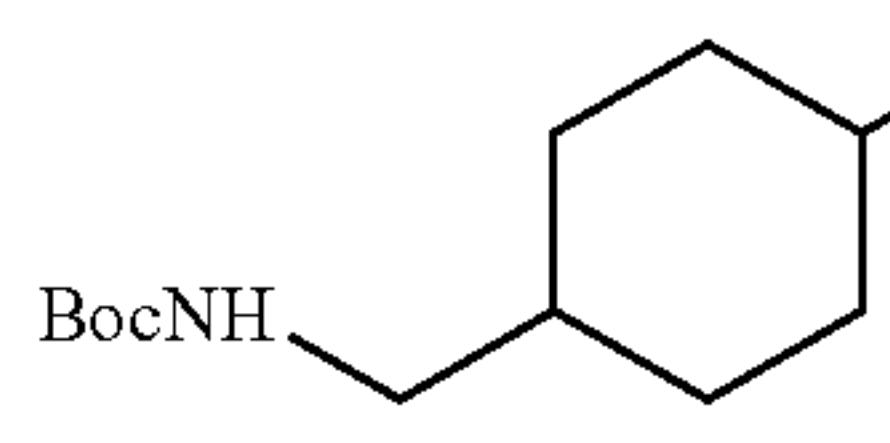
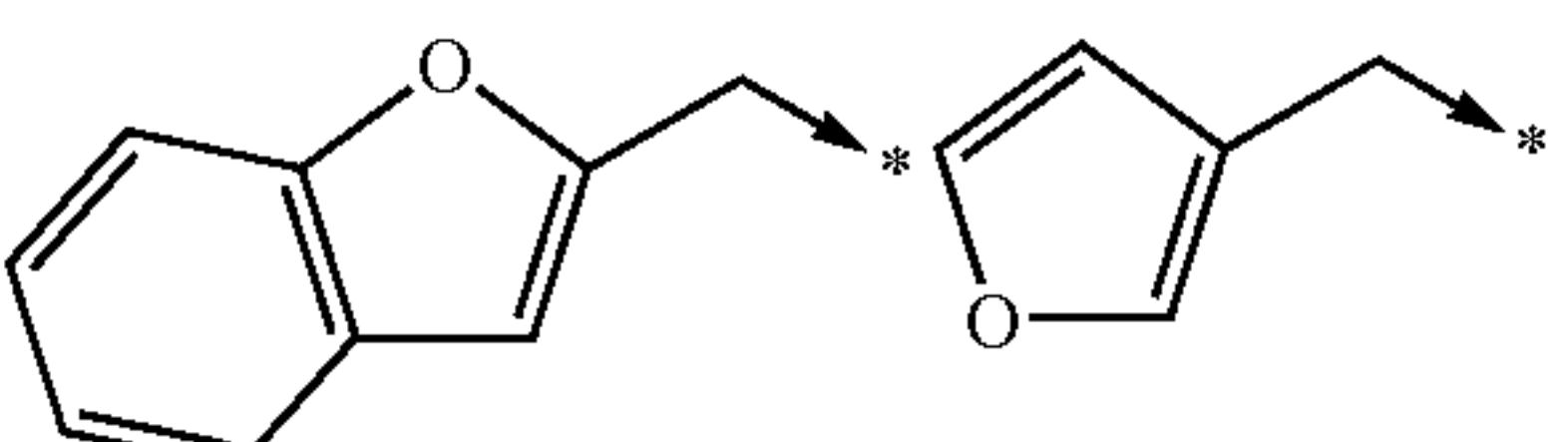
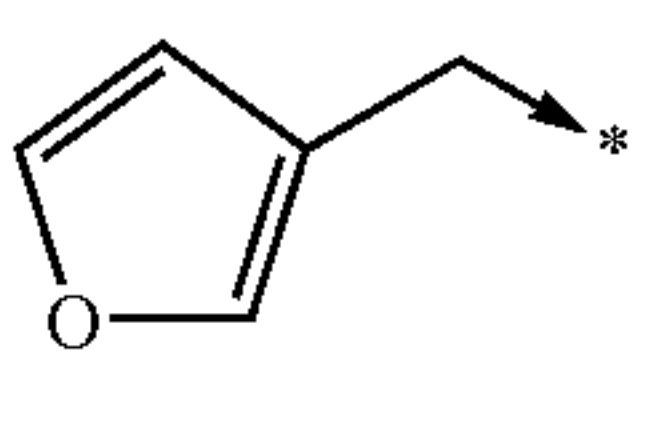
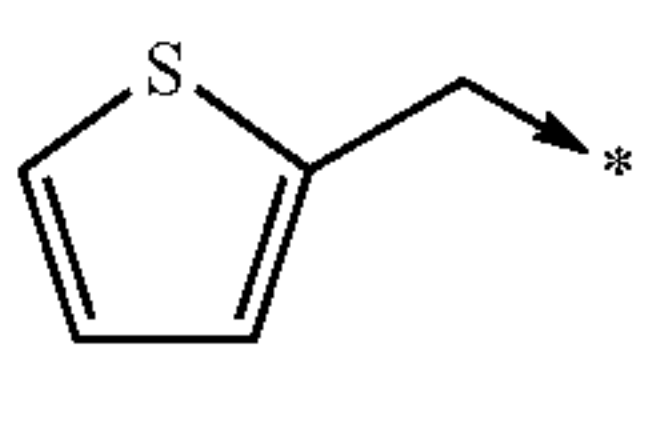
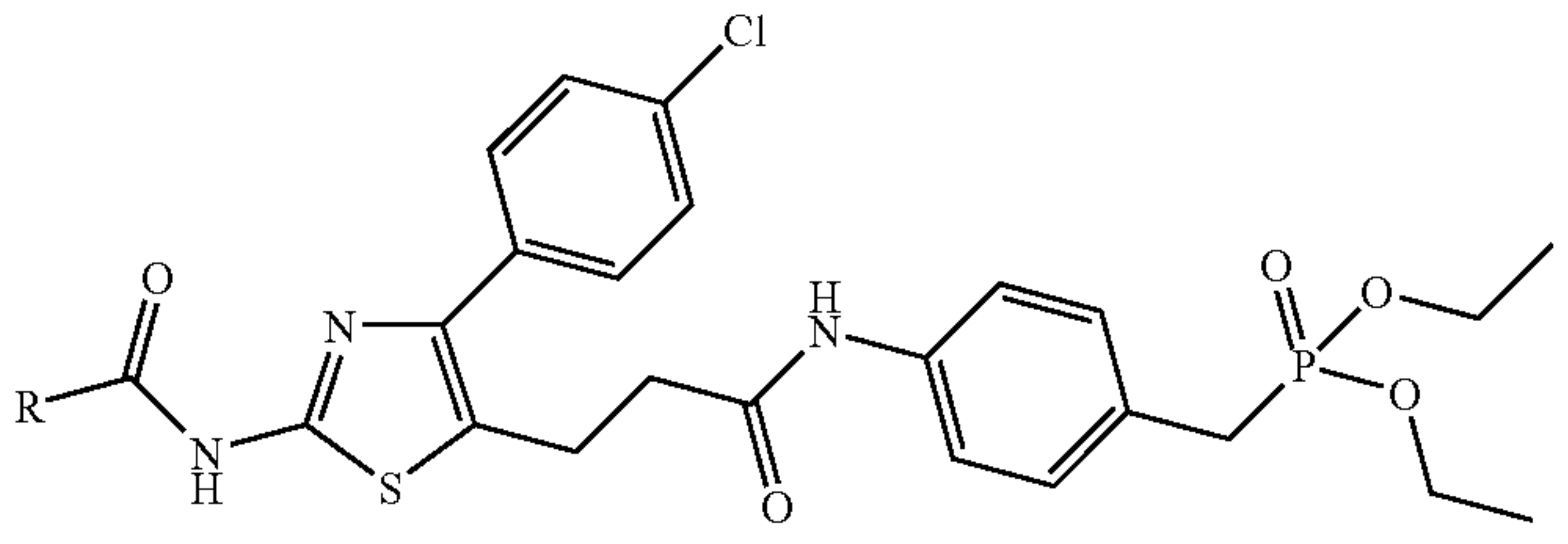
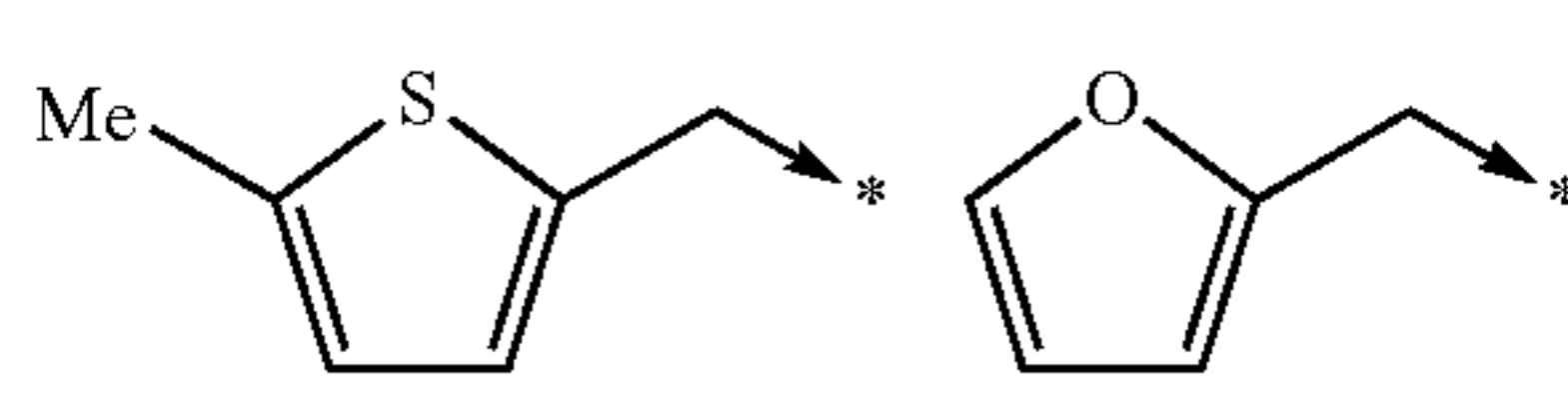
basic structure			
			
R			
			
Example 954	Example 955	Example 956	Example 957
100%, 4.413	100%, 3.447	100%, 3.982	100%, 4.259
618(M + 1)	656(M + 1)	642(M + 1)	631(M + 1)
R			
			

TABLE 18-1-continued

basic structure			
			
Example 958 99%, 4.249 747(M + 1)	Example 959 97%, 4.640 652(M + 1)	Example 960 97%, 3.996 602(M + 1)	Example 961 96%, 4.214 618(M + 1)
R			
			
Example 962 96%, 4.510 632(M + 1)		Example 963 100%, 4.137 602(M + 1)	

upper line: Example No.

middle line: HPLC purity(220 nm), retention time(min)

lower line: MS(APCI+, m/e)

TABLE 18-2

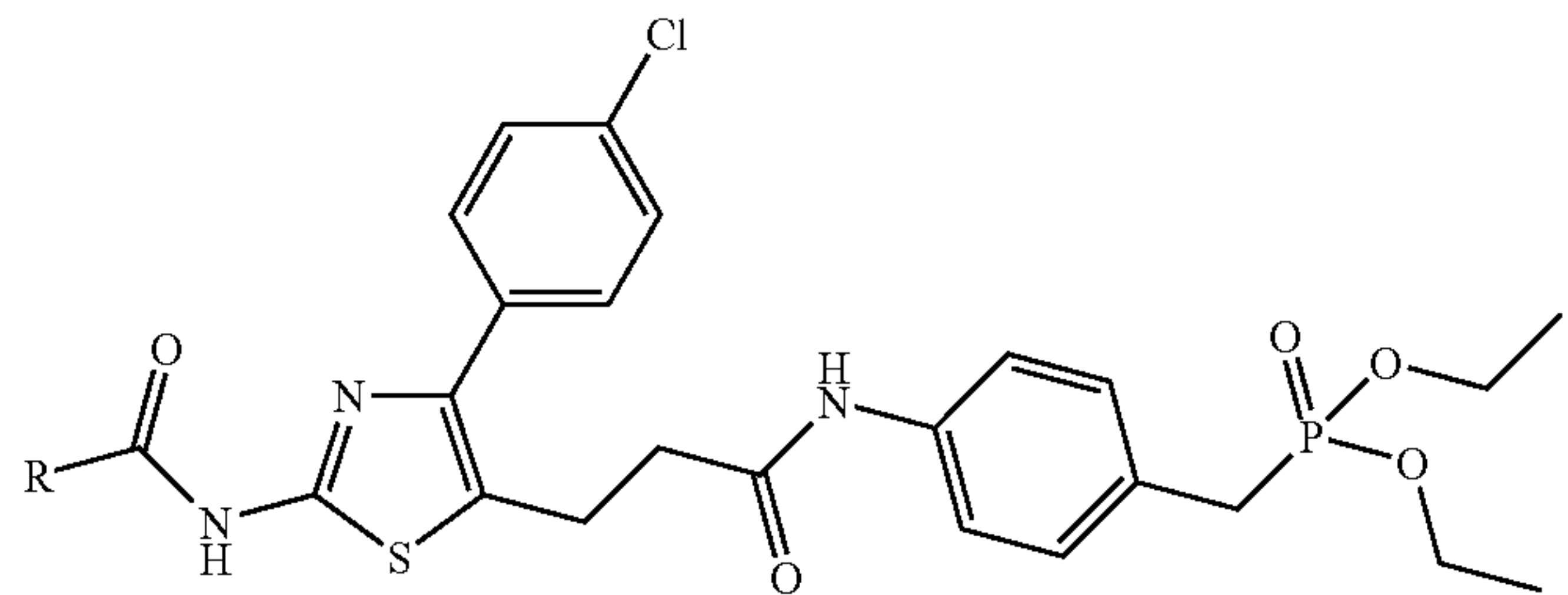
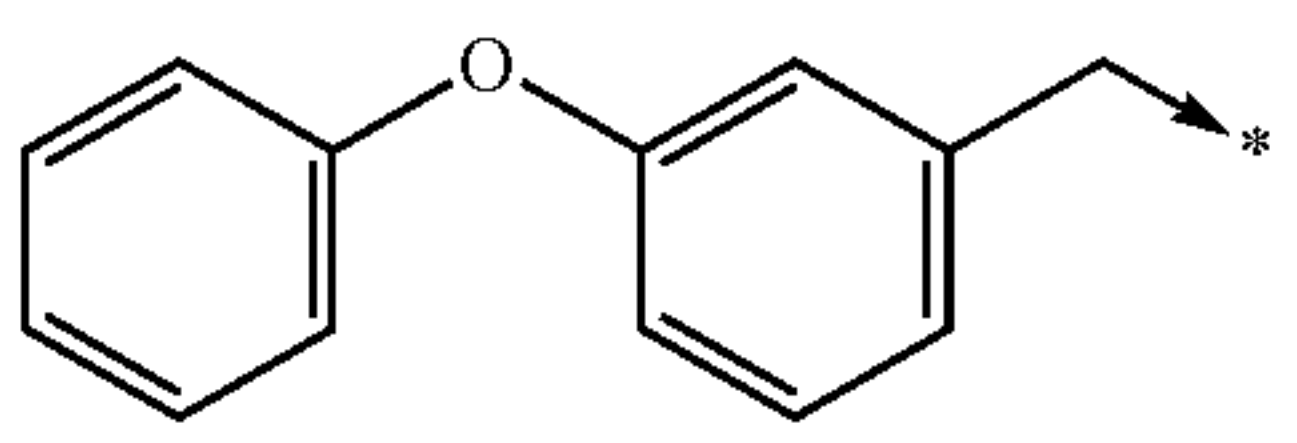
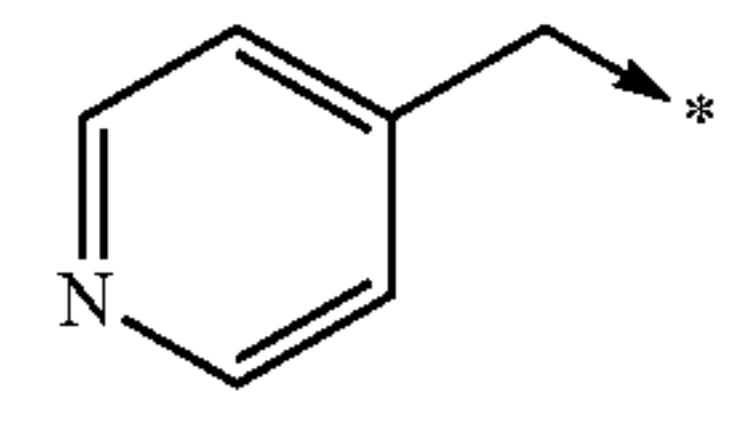
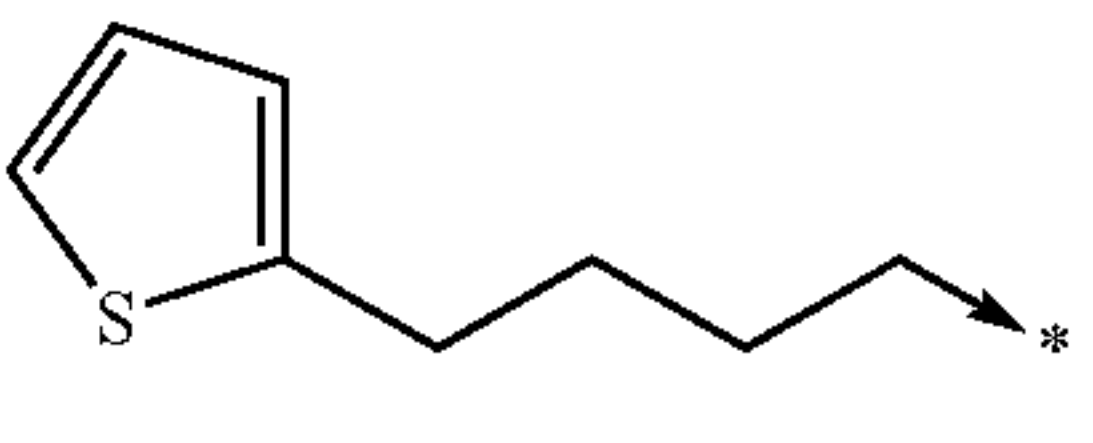
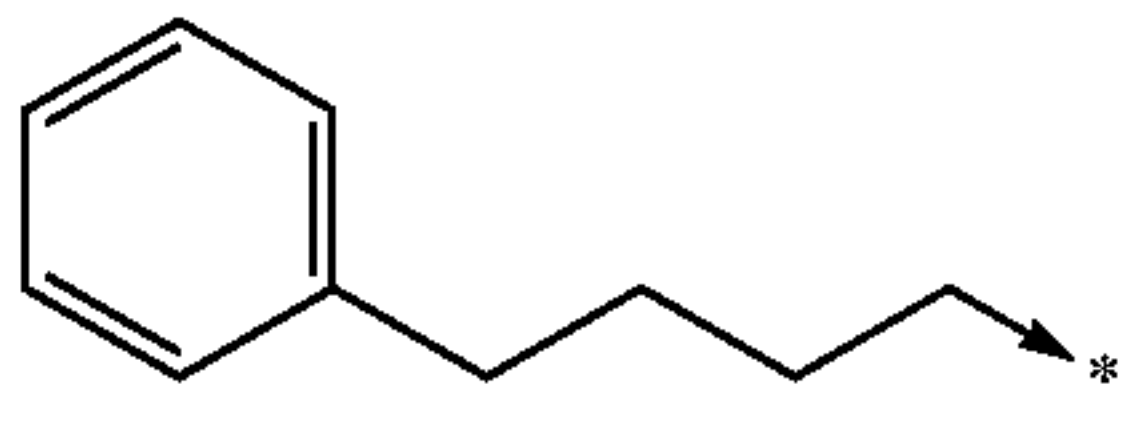
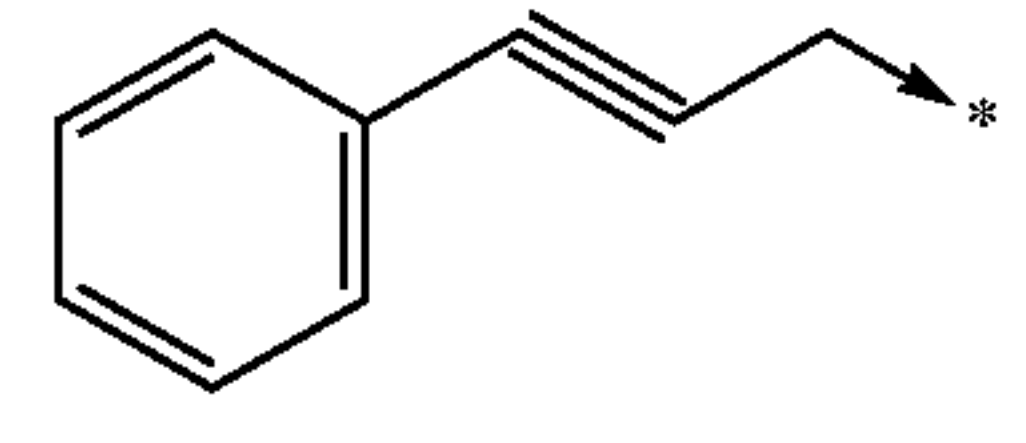
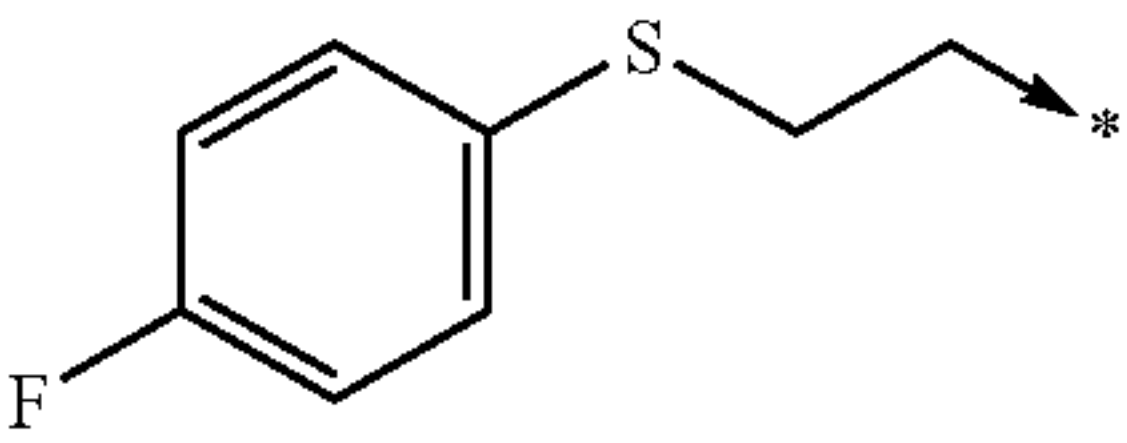
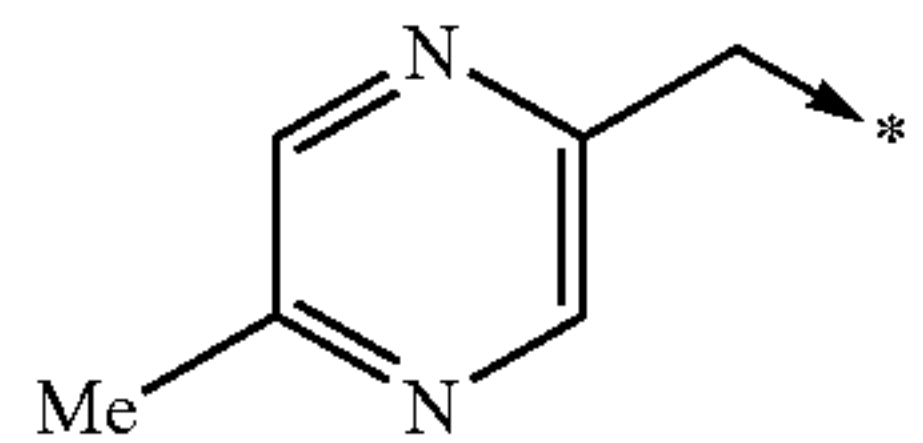
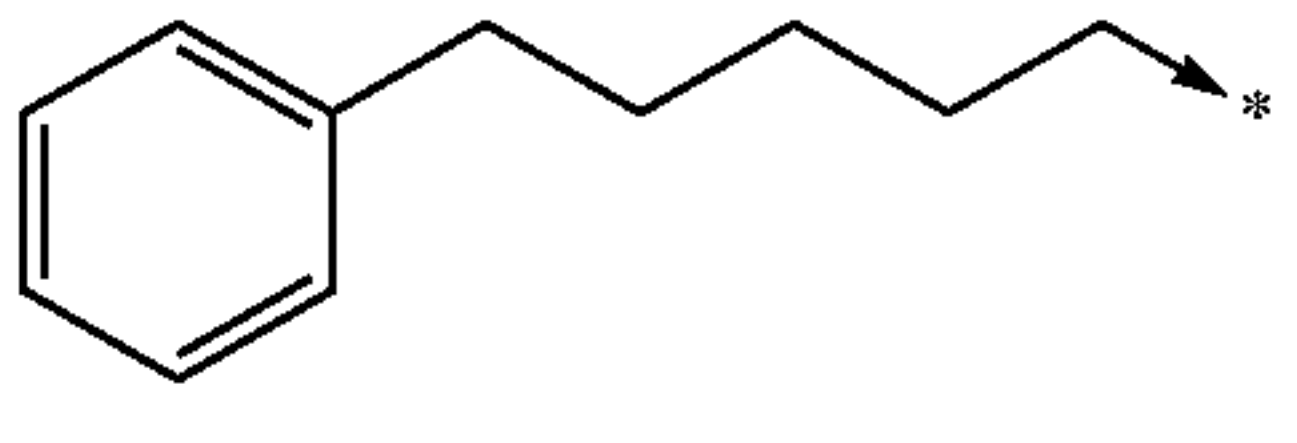
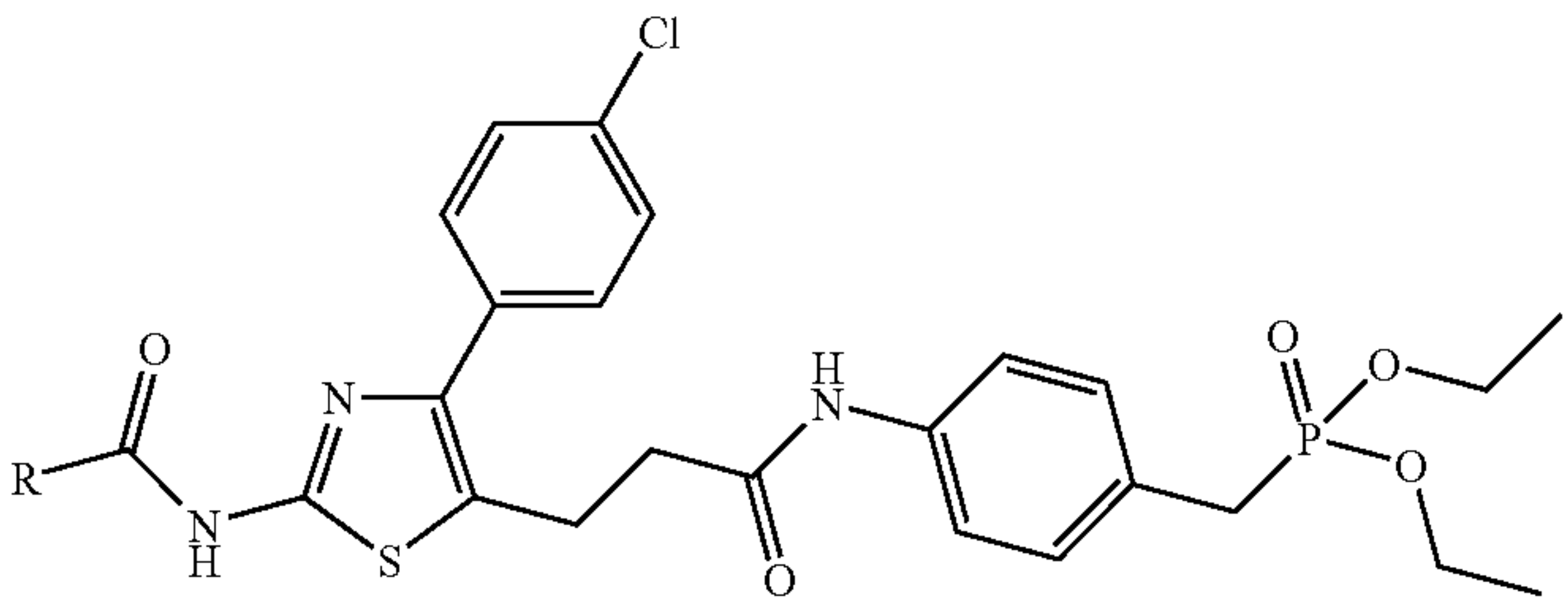
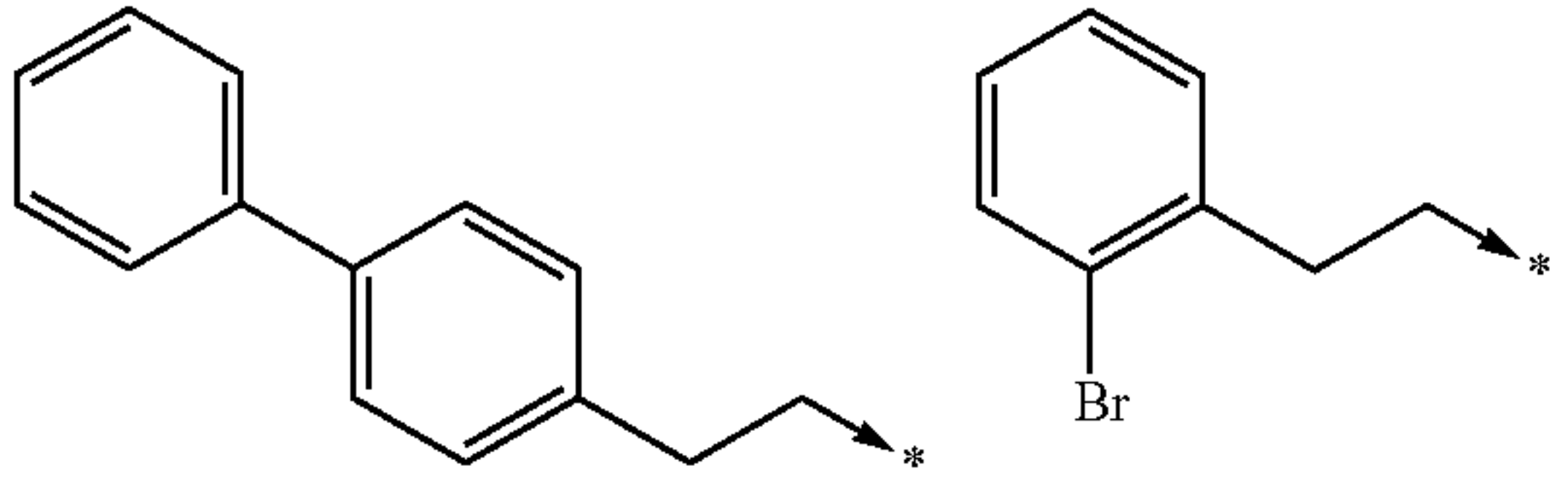
basic structure		
		
R		
		
Example 964 100%, 3.382 704 (M + 1)	Example 965 96%, 4.083 613 (M + 1)	Example 966 98%, 4.408 660 (M + 1)
R		
		
Example 969 96%, 4.507 654 (M + 1)	Example 970 99%, 4.057 636 (M + 1)	Example 971 98%, 4.470 658 (M + 1)
R		
		

TABLE 18-2-continued

basic structure		
		
Example 967 100%, 4.370 628 (M + 1)		Example 968 100%, 4.380 668 (M + 1) R
		
Example 972 98%, 4.363 702 (M + 1)		Example 973 97%, 4.118 705 (M + 1)

upper line: Example No.

middle line: HPLC purity (220 nm), retention time (min)

lower line: MS (APCI+, m/e)

TABLE 19-1

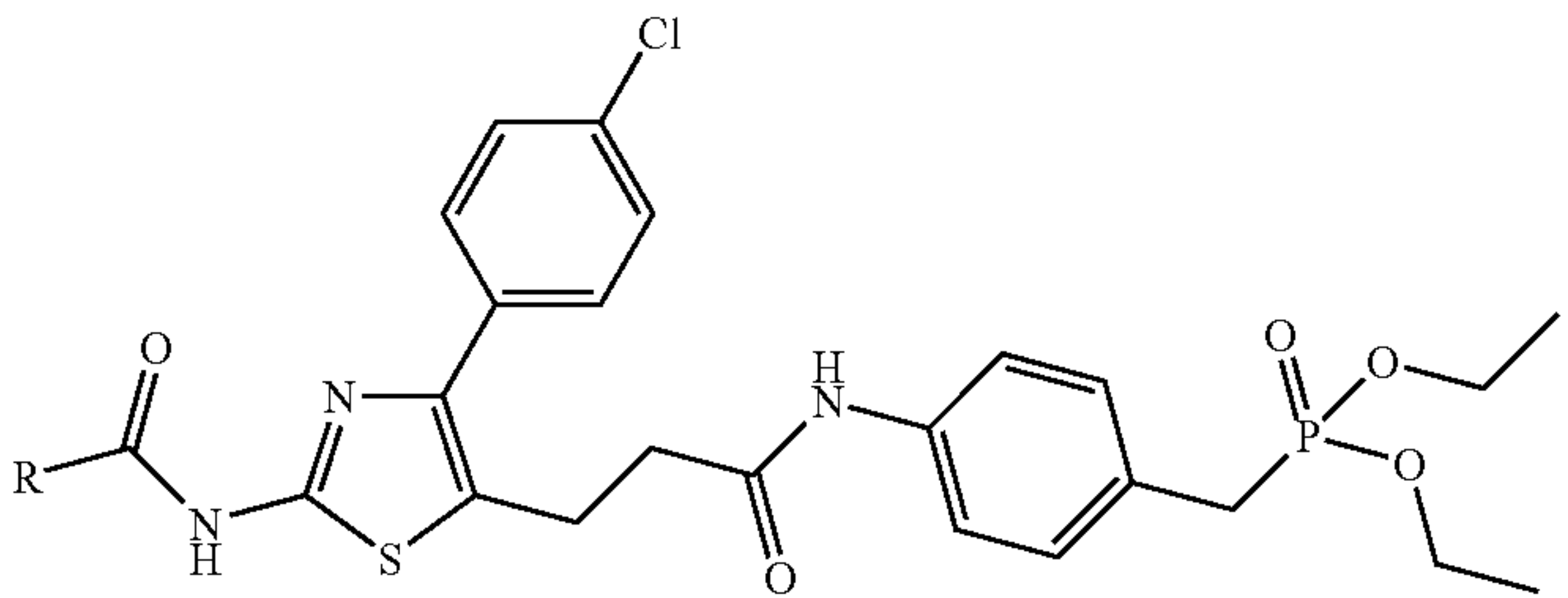
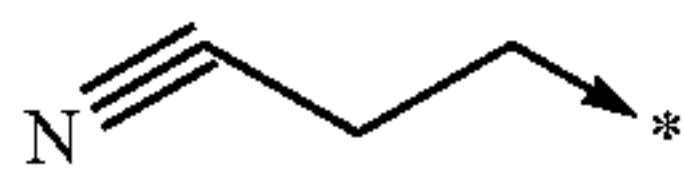
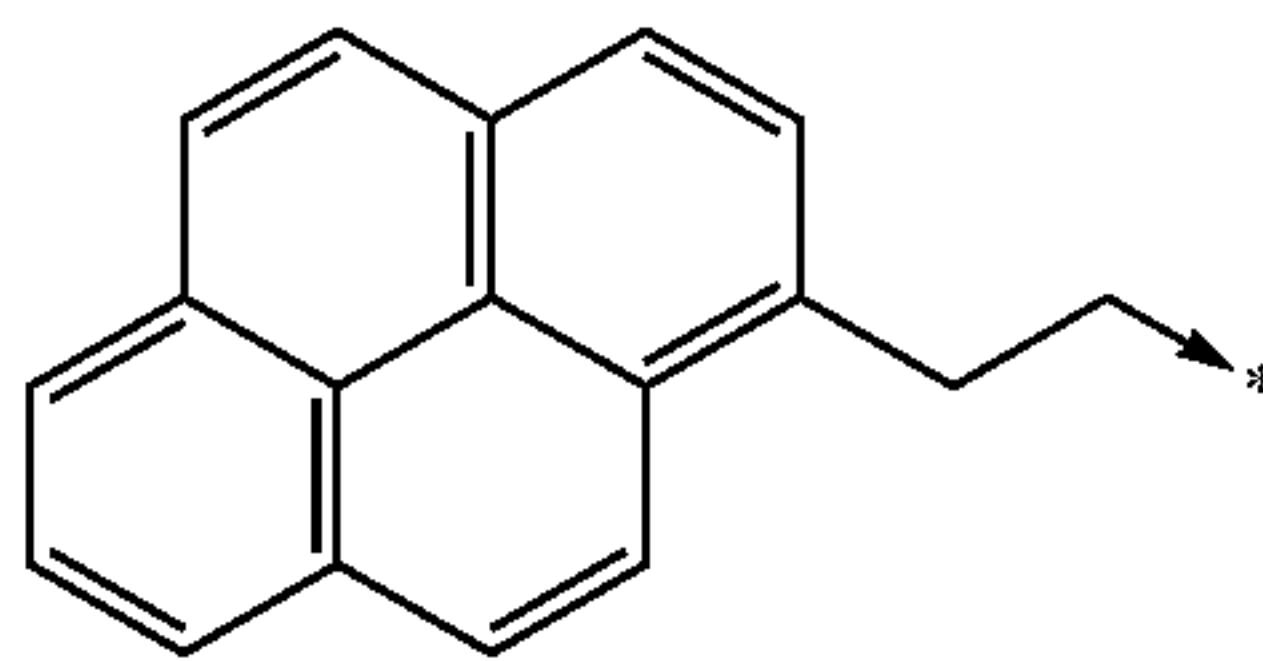
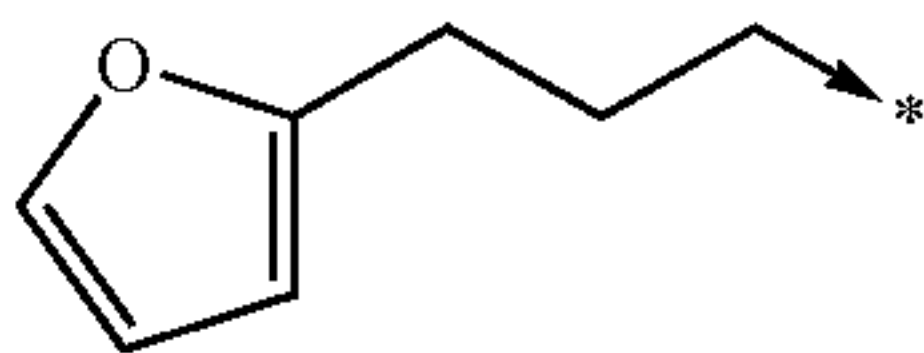
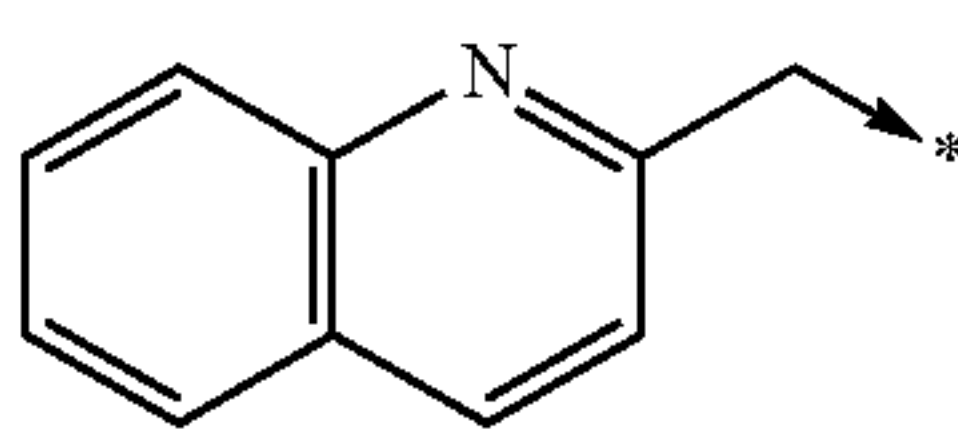
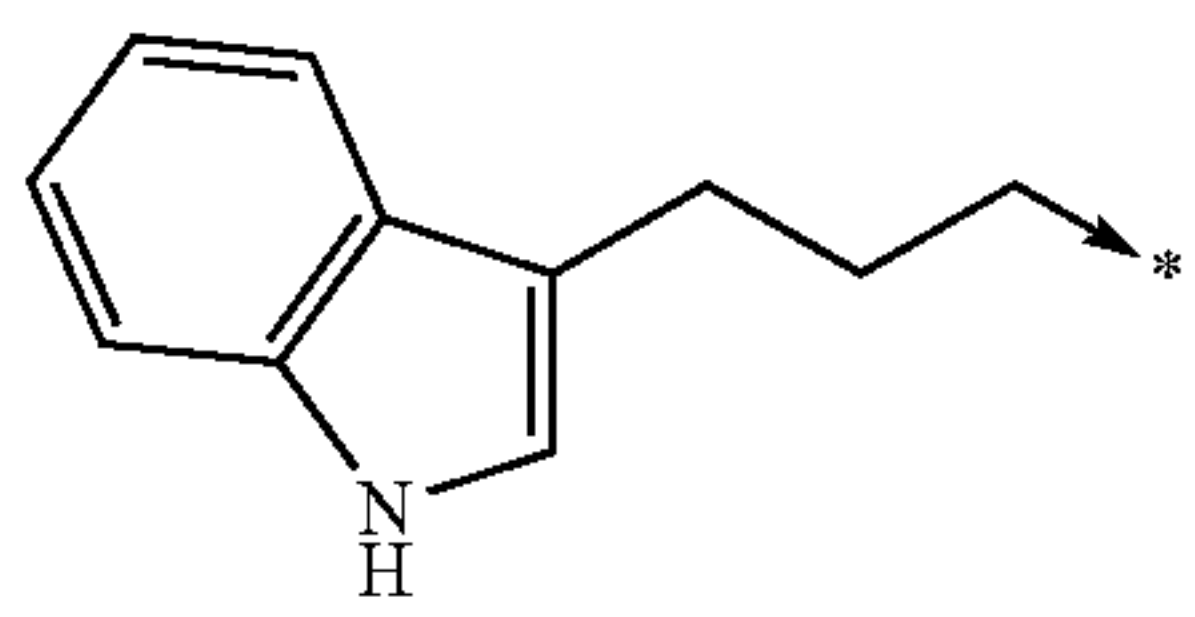
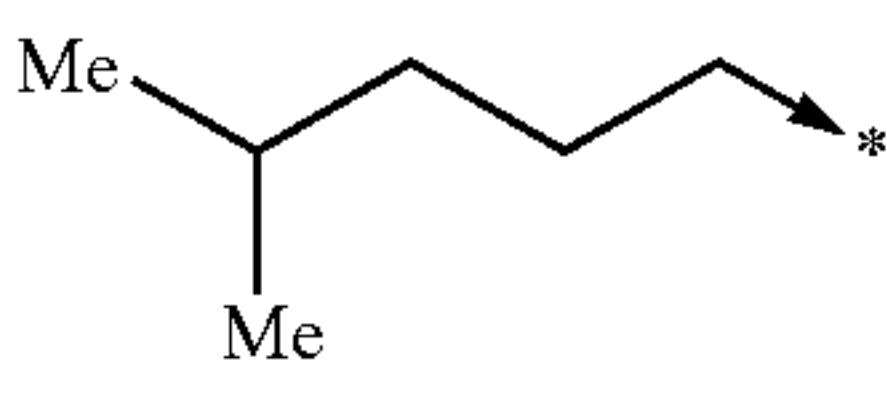
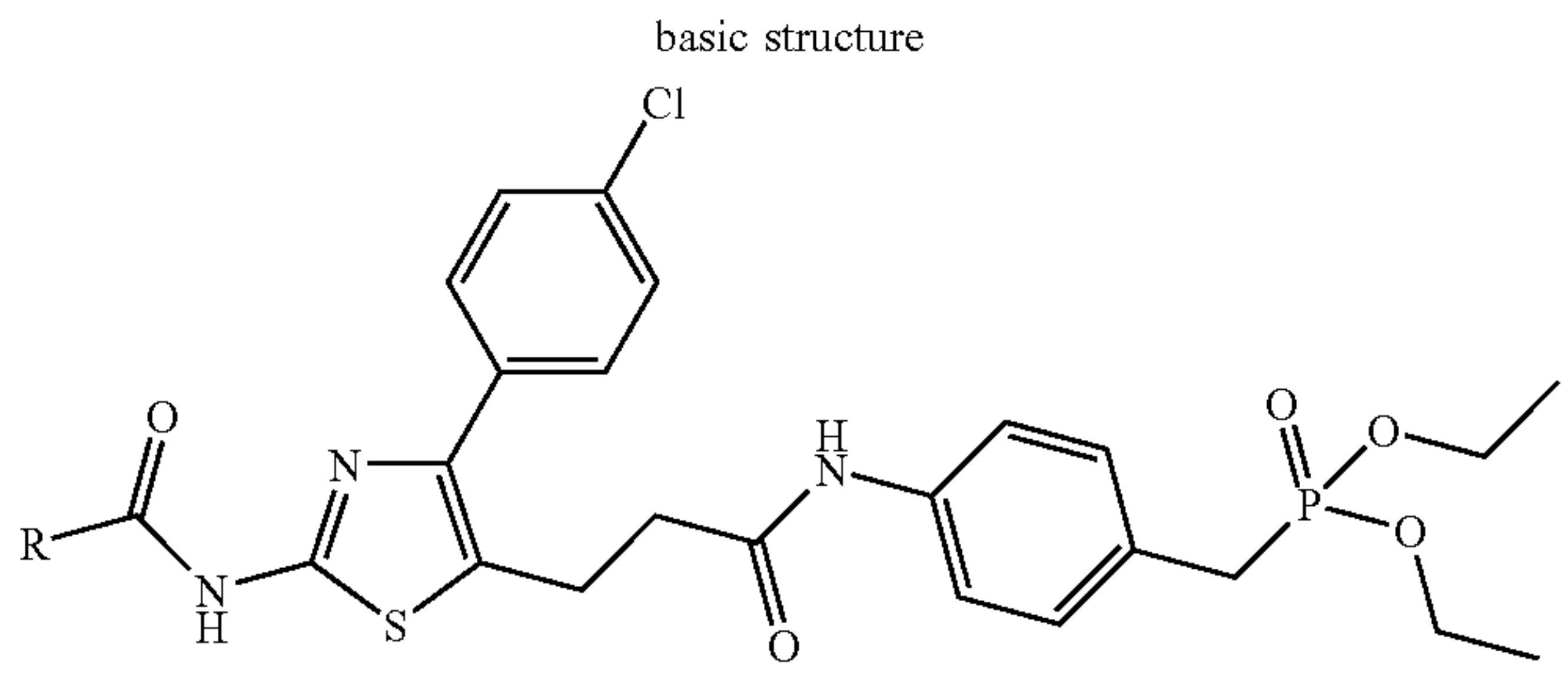
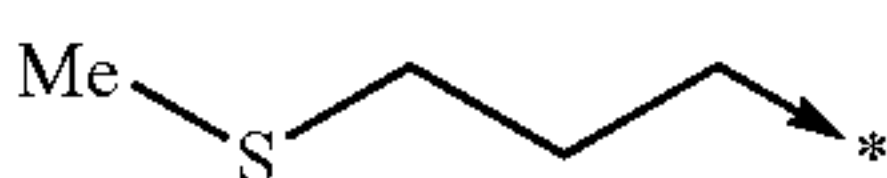
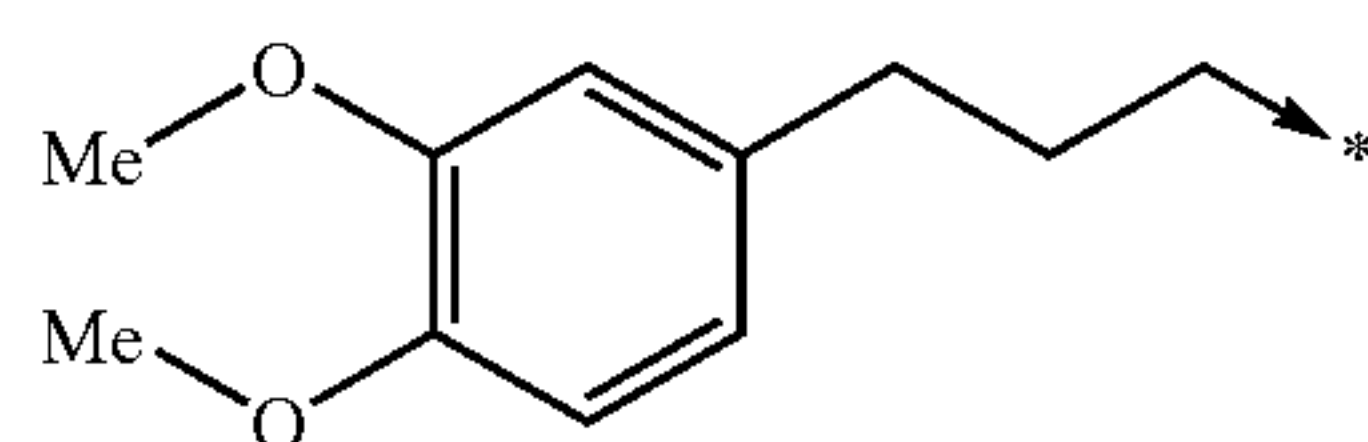
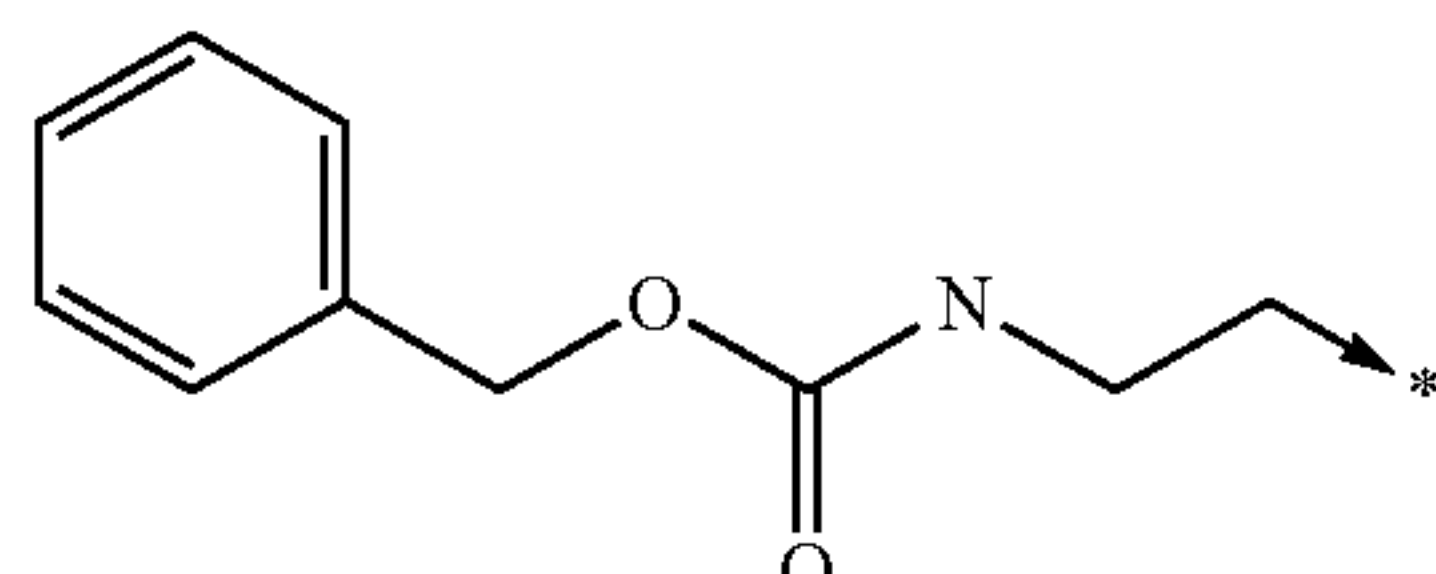
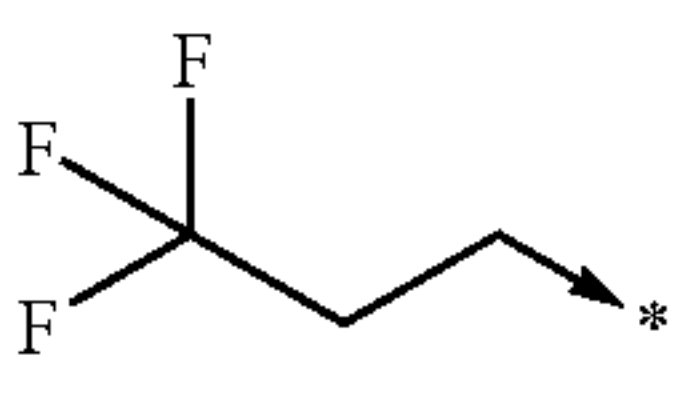
basic structure		
		
R		
		
Example 974 99%, 4.144 575 (M + 1)	Example 975 98%, 4.029 750 (M + 1) R	Example 976 98%, 4.101 628 (M + 1)
		
Example 979 93%, 4.047 663 (M + 1)	Example 980 87%, 4.460 679 (M + 1)	Example 981 100%, 4.139 606 (M + 1)

TABLE 19-1-continued

basic structure	
	
R	
	
Example 977 96%, 4.862 610 (M + 1)	Example 978 99%, 4.401 700 (M + 1)
R	
	
Example 982 100%, 4.810 699 (M + 1)	Example 983 100%, 4.136 618 (M + 1)

upper line: Example No.

middle line: HPLC purity (220 nm), retention time (min)

lower line: MS (APCI+, m/e)

TABLE 19-2

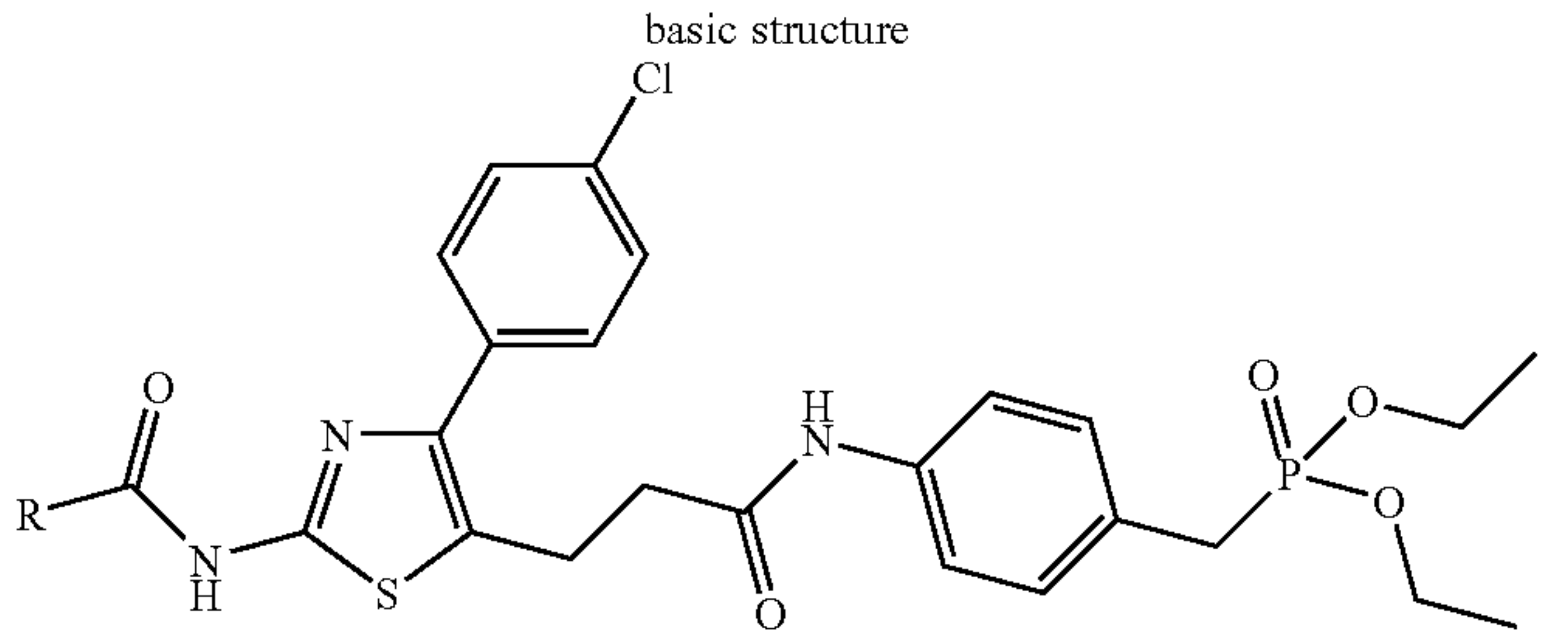
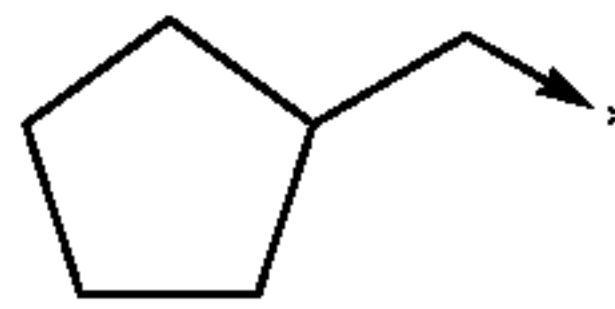
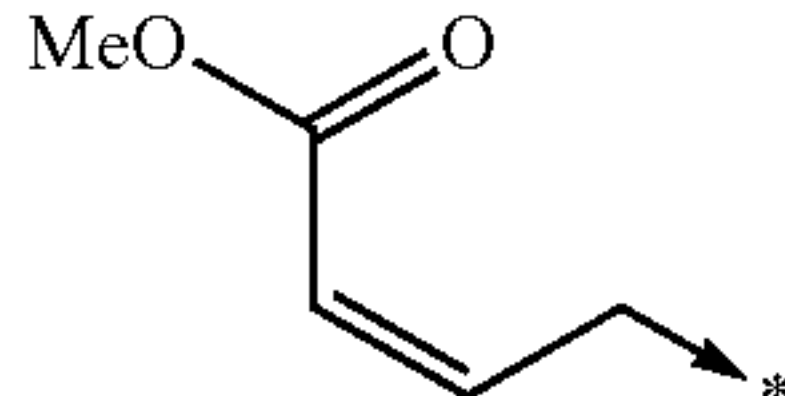
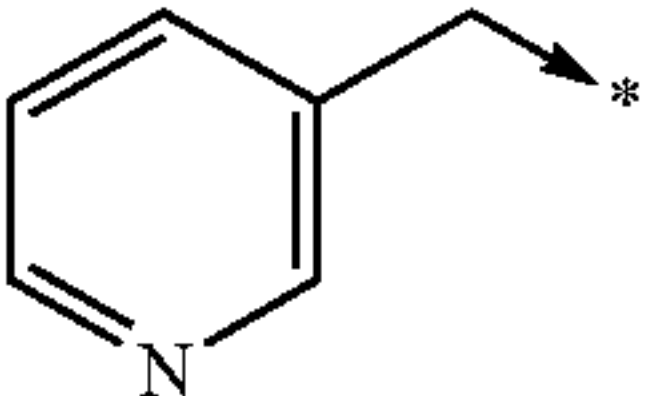
basic structure		
		
R		
		
Example 984 100%, 4.254 604 (M + 1)	Example 985 100%, 4.071 620 (M + 1)	Example 986 99%, 4.806 613 (M + 1)
R		

TABLE 19-2-continued

basic structure		
Example 989 97%, 4.296 723 (M + 1)	Example 990 99%, 4.281 680 (M + 1)	Example 991 99%, 3.808 614 (M + 1)
R		
Example 987 98%, 4.411 679 (M + 1)	Example 988 100%, 4.346 702 (M + 1)	R
Example 992 99%, 4.113 680 (M + 1)	Example 993 98%, 4.586 666 (M + 1)	

upper line: Example No.

middle line: HPLC purity (200 nm), retention time (min)

lower line: MS (APCI+, m/e)

Experimental Example 1

To 6-week-old male SD rats (CLEA Japan, Inc.) was injected 70 mg/kg body weight of streptozotocin (STZ) from the tail vein to form a diabetic neuropathy model.

After raising for one month, 3 mg/kg of compound (compound of Example 5 or Example 226) suspended in 0.5% methyl cellulose was orally administered to the rats. For the control group, a 0.5% aqueous methyl cellulose suspension free of the aforementioned compound was administered.

After the completion of the administration, the rats were anesthetized with Nembutal, the body temperature was maintained at a constant level using a hot plate at 37° C. and a desk lamp, needle electrodes were placed on the above-knee region and ankle, stimulated using Neuropack 2 (NIHON KOHDEN CORPORATION) principally at 1.6 mA

50 and the evoked potential was detected from the plantar part. The Motor Nerve Conduction Velocity (MNCV) was calculated from the distance between different electrodes and latency difference of waveforms.

55 After the evaluation of the nerve conduction velocity, the ischiadic nerve was taken from the rat, a lysis buffer (0.1M Tris-HCl buffer containing 1M sodium chloride, 2% BSA, 2 mM EDTA, 80 trypsin unit/L of aprotinin, pH 7.6) in a 20-fold amount of the wet weight of ischiadic nerve was added and the mixture was subjected to ultrasonication and centrifugal separation (15,000 rpm, 60 min.), and the BDNF content of the supernatant was measured.

65 The BDNF content was measured by sandwich ELISA Method using anti-BDNF polyclonal antibody (Promega) and biotinated anti-BDNF antibody (G1641, Promega). The results are shown in [Table 20].

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TABLE 20

	MNCV (m/s)	BDNF (ng/g)
control group	45.1 ± 4.4	2.0 ± 0.4
Compound of Example 5 administration group	52.7 ± 5.0**	2.6 ± 0.7**
Compound of Example 226 administration group	52.3 ± 2.4**	3.6 ± 0.4*

average value ± SD (n = 7-8)

*p < 0.05 vs. control group (t-test)

**p < 0.01 vs. control group (t-test)

As shown in [Table 20], the compound of the present invention increased motor nerve conduction velocity and nerve BDNF content.

Formulation Example 1 (Production of Capsule)

1) compound of Example 1	30 mg
2) cellulose fine powder	10 mg
3) lactose	19 mg
4) magnesium stearate	1 mg
total	60 mg

1), 2), 3) and 4) are mixed and filled in gelatin capsules.

Formulation Example 2 (Production of Tablet)

1) compound of Example 1	30 g
2) lactose	50 g
3) corn starch	15 g
4) carboxymethylcellulose calcium	44 g
5) magnesium stearate	1 g
1000 tablets total	140 g

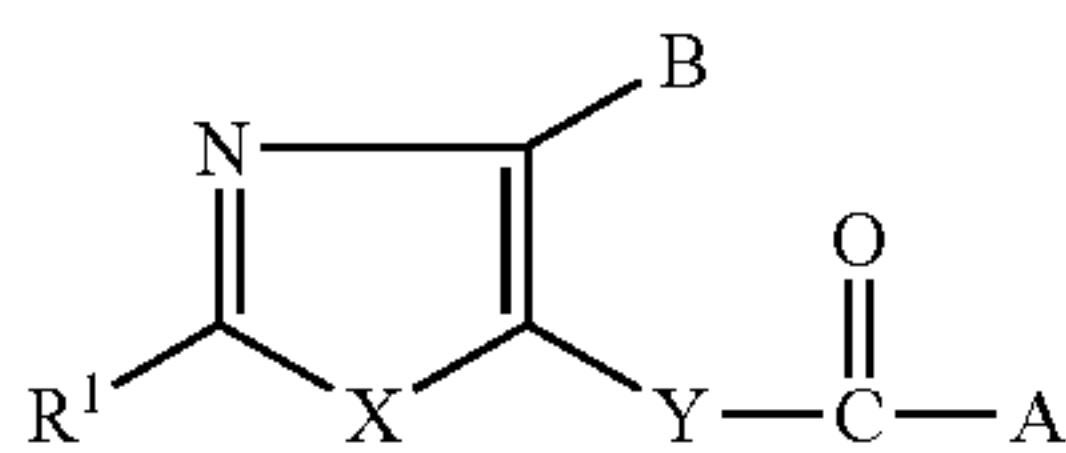
The total amount of 1), 2) and 3) and 30 g of 4) are kneaded with water and, after drying in vacuo, granulated. The granules are mixed with 14 g of 4) and 1 g of 5) and punched with a tableting machine. In this way, 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

INDUSTRIAL APPLICABILITY

The compound of the present invention has a superior action of promoting production or secretion of a neurotrophic factor, and is useful for the prophylaxis or treatment of diabetic neuropathy and the like.

The invention claimed is:

1. A compound represented by the formula (I)



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wherein R¹ is an optionally substituted heterocyclic group,

A is an optionally substituted cyclic amino group or —NR²—W—D wherein P² is a hydrogen atom or an alkyl group,

W is a bond or a divalent acyclic hydrocarbon group,

D is an optionally substituted cyclic group, an optionally substituted amino group or an optionally substituted acyl group,

B is an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group,

X is an oxygen atom, and

Y is a bond or a divalent acyclic hydrocarbon group, or a salt thereof.

2. The compound of claim 1, wherein A is an optionally substituted cyclic amino group.

3. The compound of claim 1, wherein A is —NR²—W—D wherein R² is a hydrogen atom or an alkyl group, W is a bond or a divalent acyclic hydrocarbon group, and D is an optionally substituted cyclic group, an optionally substituted amino group or an optionally substituted acyl group.

4. The compound of claim 3, wherein D is an optionally substituted cyclic group.

5. The compound of claim 1, wherein B is an optionally substituted C₆₋₁₄aryl group.

6. The compound of claim 1, wherein Y is C₁₋₄alkylene.

7. The compound of claim 1, which is 3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide;

3-[4-(4-chlorophenyl)-2-(4-morpholinyl)-5-oxazolyl]-N-[4-(diethylphosphonomethyl)phenyl]propionamide;

3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-{4-[(2-oxide-1,3,2-dioxaphosphinan-2-yl)methyl]phenyl}propionamide;

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[(4-dimethylphosphonomethyl)phenyl]butanamide;

1-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}-4-piperidinol;

4-{3-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide;

4-[2-(1H-benzimidazol-1-yl)-4-(4-chlorophenyl)-5-oxazolyl]-N-[(4-diethylphosphonomethyl)phenyl]butanamide; or

4-{3-[4-(4-chlorophenyl)-2-(1-methyl-1H-indol-3-yl)-5-oxazolyl]propanoyl}thiomorpholine-1,1-dioxide.

8. A pharmaceutical agent comprising the compound of claim 1 or a prodrug thereof and a pharmaceutically acceptable carrier, excipient or diluent.

9. A method for the treatment of diabetic neuropathy in a mammal in need thereof, which comprises administering an effective amount of compound of claim 1 or a prodrug thereof to the mammal.

10. A method for the treatment of pain in a mammal in need thereof, which comprises administering an effective amount of compound of claim 1 or a prodrug thereof to the mammal.

* * * * *